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Uncovering Creutzfeldt-Jakob Disease: The Mysteries of Prion Diseases

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ABSTRACT

Neurodegenerative diseases are very common around the world and happen due to a variety of reasons. Some of them happen due to old age, some of them might occur due to external factors, etc. Though rare, prion diseases are a type of neurodegenerative disease that are caused by prions, hence the name. Prions are intrinsically disordered proteins that cause other proteins around them to fold and are transmissible through different media like food and genetics. Prions are quite similar to viruses in that they are contagious but are functionally different from each other. Unlike viruses, prions can actually clump up in the brain and damage neural cells that way. Though these diseases are rare, there are many scientists around the world experimenting and researching possible treatments for them as there are none right now. The mysteries of prion diseases are what makes them so confounding; they are quite unpredictable and can even occur in the healthiest people. Unraveling these mysteries will help aid society to find cures for these diseases and improve the lives of many around the world.

Introduction

Neurodegenerative diseases are diseases that gradually damage the nervous system (Cleveland Clinic, 2023). This broad spectrum of diseases breaks down into multiple subsections, which are: dementia-type diseases, demyelinating diseases, motor neuron diseases, parkinsonism-type diseases, and prion diseases. Most of these diseases damage the neurons in the brain, which therefore affects vital functions of the body, such as movement. Prion diseases are one type of neurodegenerative disease which are caused by prions. Prions are a type of protein that can cause other proteins to fold abnormally and affects both humans and animals (Hopkins Medicine, n.d). These prions start to clump in the brain and cause brain damage which can lead to memory problems, personality changes, and other symptoms. These symptoms are quite reflective of the other types of neurodegenerative diseases but unlike the others, prion diseases are often fatal.

Bovine spongiform encephalopathy (also known informally as mad cow disease) is a type of prion disease that affects cows. These cows contracted BSE by being fed meat-and-bone meals that contained prion-infected products (CDC.gov, 2024). The cattle, which were now affected with BSE, were then fed to humans, and no amount of cooking can truly remove these prions from the meat. This contraction is one of the ways humans can get a prion disease, but they can also get it due to family history, or being infected by medical equipment.

One of the main prion diseases which affects humans is Creutzfeldt-Jakob disease. There are three main types of CJD: sporadic (sCJD), genetic (or familial), and acquired (variant CJD and iatrogenic CJD), which are described in the section below. This prion disease leads to the symptoms that can sometimes be confused for Alzheimer's disease. Other symptoms include jerking movements, insomnia, blurry vision, and more. The symptoms start to rapidly get worse as one is affected by CJD; they worsen over a period of several weeks or a few months (Mayo Clinic, 2023). It is usually fatal within a year but patients do not die due to the disease itself; they die due to issues related to the disease, such as having trouble swallowing, lung failure, heart issues, or other causes. In 2013, an article described a 66-year-old woman who was characterized with a 5-month history of progressive dementia. After further tests, she

was diagnosed with sCJD. She was then seen with all of the common symptoms: blurry vision, progressive dementia, and more. As is common with other cases of CJD in general, the symptoms worsened and she passed away 7 months after the initial onset of the disease (Kojima et al., 2013). The case study discusses how CJD mimics other neurodegenerative diseases, such as Alzheimer's, in the context of their symptoms. This case study shows how dangerous and fatal this disease can be in such a short amount of time. CJD is a very rare disease; one or two people in every million are affected, but the cases are very serious. There is no way to treat it in itself, but there are medications that one can take to lessen the symptoms. In addition, there is limited research done on the foundation of this disease. Diagnosing CJD is often difficult as it reflects the symptoms of other neurodegenerative diseases, so uncovering the foundations behind this prion disease will aid in informing and educating people and change society for the better.

Methodology

The purpose of this paper is to thoroughly provide an explanation of Creutzfeldt-Jakob disease and discuss the effects & possible treatments of the disease. The method used to write this paper is data collection, using search engines such as Google Scholar to find a variety of journal articles and excerpts from texts which were related to this topic. Keywords, such as "Creutzfeldt-Jakob disease", "CJD pathology", and more, were used to search for articles related to this disease. These keywords were vital in finding adequate sources that were based on this disease as there was not much done initially. To write a thorough literature review, this paper depended on these articles and studies to provide accurate data and information. In addition, these sources were used to explain CJD and other derivatives of this prion disease. Analyzing different sources that are made from different experiences helps to factor in different perspectives and makes sure that each perspective is clearly discussed to help draw conclusions that will help explain this rare disease and its possible treatments.

Proteins

Proteins are large molecules, consisting of long chains of amino acids, and the sequences of the amino acids are determined by the DNA in the cell (NIH, 2024). Proteins can be used by the body for many different functions, such as structural support, hormones, and initiating apoptosis (programmed cell death). Proteins have levels of structures, which shows the progression of its formation, starting from the mRNA carrying the amino acid sequences, the tRNA carrying amino acids to the ribosomes, the structure for the polypeptides, and its folding.

Amino Acids

Amino acids are molecules that combine to make up a protein. There are many different types of naturally occurring amino acids, but only 20 of them are essential to the human body: valine, tyrosine, tryptophan, threonine, serine, proline, phenylalanine, methionine, lysine, leucine, isoleucine, histidine, glycine, glutamine, glutamic acid, cysteine, aspartic acid, asparagine, arginine, and alanine (Lopez & Mohiuddin, 2024). There are three different categories of these amino acids needed by the body, ranked in terms of how essential they are to live:

Essential Amino Acids

These amino acids cannot be synthesized by mammalian cells. There are 9 essential amino acids: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine (Lopez & Mohiuddin, 2024).

Conditionally Essential Amino Acids

These amino acids are not usually essential. There are exceptions to this, including illness and stress. There are 7 conditionally essential amino acids: arginine, cysteine, glutamine, tyrosine, glycine, proline, and serine (MedlinePlus, 2023).

Non-Essential Amino Acids

These amino acids are not essential in the context that they can be produced by the human body (and therefore, do not need to be consumed through food). There are 4 non-essential amino acids, in addition to the 7 conditionally essential amino acids: alanine, asparagine, aspartic acid, and glutamic acid.

All amino acids follow the same fundamental structure; a central carbon atom, or the α (alpha) carbon, which is bonded to an amino group (NH_2), a carboxyl group (COOH), and a hydrogen atom (LumenLearning, n.d). When a cell is in an aqueous (in water) environment, in physiological conditions (where the pH is around 7.4), the amino group and carboxyl group are ionized and therefore become $-NH_3^+$ and $-COO^-$, respectively (the hydrogen is deprotonated, or removed of its proton, and is sent to the amino group). Each amino acid also has another atom or a group of atoms bonded to the α carbon, known as the *R* group. The *R* group, also known as the side chain of an amino acid, gives the amino acids specific characteristics (such as pH, polarity, and size). Figure 1A below shows the foundational structure of an amino acid. All of the bonds in an amino acid are single bonds, except for one double bond in the carboxyl group. The difference in the structures which gives each amino acid its individuality is the side chain; its properties determine the characteristics of the amino acid.

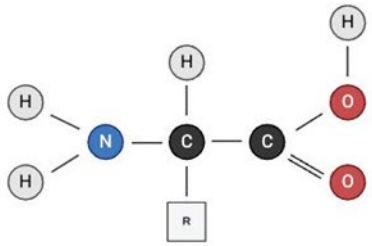

Figure 1A. Structure of a generic amino acid. Source: Nair, 2024 (Figure created in BioRender.com). Description: The nitrogen in the amino group can also be described as *α-amine* and the carbon in the carboxyl group can be described as the *α-carboxyl*; these names can be used as a way to distinguish them from certain similar-named groups present in the side chain.

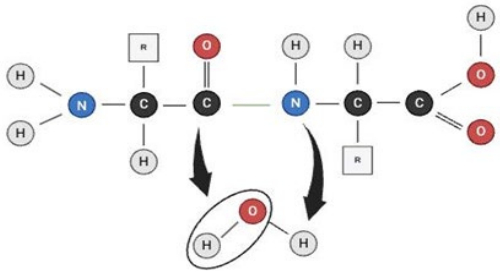

Figure 1B. Structure of two generic amino acids and a peptide bond in between (light green). Source: Nair, 2024 (Figure created in BioRender.com)**.** Description: The OH^- from the carboxyl group of one amino acid and the hydrogen from the amino group of the other is removed to form H_2O, or water. Amino acids form a polypeptide chain (otherwise known as a protein) through the formation of peptide bonds.

Protein Formation & Structure

Proteins start forming when the genes in a cell's DNA are transcribed into mRNA (messenger RNA) molecules, which are transported out of a cell's nucleus into the cytoplasm. These molecules contain protein information such as amino acid sequences. They are transported to the cell's ribosomes, which read the mRNA's nucleotide sequence & codons (a sequence of three nucleotides; each one codes for a specific amino acid) in order to send it to the tRNA (transfer RNA). The tRNA starts assembling the polypeptide chain (with each amino acid, one by one) and only stops when the ribosome finds a stop codon, which does not code for an amino acid (MedlinePlus, n.d).

Once the tRNA is done forming the polypeptide chain, it creates the first level of structure, which is called the primary structure of a protein. There are three more levels of protein structure, which are affected in accordance with the interactions between what is contained in a protein & the protein itself. The three levels are: secondary structure, tertiary structure, and quaternary structure.

The secondary structure of a protein is affected due to the backbone of a polypeptide chain. The bonds between the polypeptide chains can form three structures:

Parallel B-Pleated Sheet

Two or more polypeptide chains line up, forming hydrogen bonds between the backbones in a parallel arrangement (LibreTexts, n.d).

Anti-Parallel B-Pleated Sheet

Two or more polypeptide chains line up, forming hydrogen bonds between the backbones in a reflective (or reversive) fashion (LibreTexts, n.d).

Alpha-Helix Sheet

The polypeptide chain is arranged in a spiral and the backbone forms hydrogen bonds with each other (The University of Vermont, n.d).

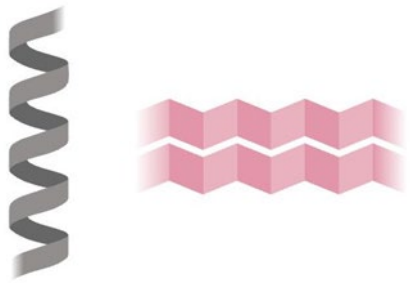

Figure 2A. Structures representing an α-helix and a β-pleated sheet**.** Source: Nair, 2024 (Figure created in BioRender.com). Description: The α-helix structure is on the left, and the β-pleated sheet is on the right. These structures are all affected by different criteria such as whether a protein's amino acids might be hydrophobic or not, etc.

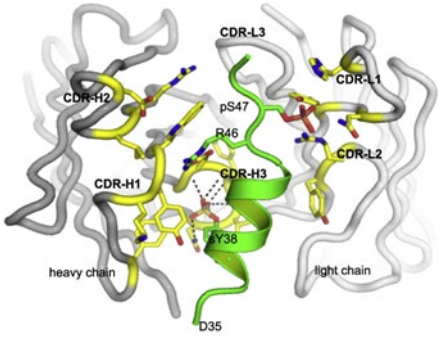

Figure 2B. Figure representing an intrinsically disordered protein. Source: Ultsch et al., 2019. Description: As seen, there is no defined structure in this protein and is therefore unstructured or disordered.

The tertiary structure of a protein is affected due to the interactions between the side chains of the amino acids in a polypeptide chain. These interactions can include bonds between side chains or bonds between a side chain and a backbone as well (Rehman et al., 2024). Bonds such as hydrogen bonds, ionic bonds, and other intermolecular forces can occur. An amino acid named cysteine (conditionally essential/non-essential) contains sulfur in its sidechain, and the tertiary structure of a polypeptide chain which contains cysteine can have a disulfide bond in the side chain (Weiss et al., 2022). This bond is the strongest bond out of the bonds which can contribute to a tertiary structure.

Finally, the quaternary structure of a protein is when multiple polypeptide chains join together to form a closely packed arrangement of proteins, also known individually as a subunit (Ouellette et al., 2015). When subunits come together, they form the quaternary structure of a protein. The interactions between each subunit are mostly weak intermolecular forces (similar to some of the interactions in the tertiary structure) and therefore is easier to be denatured, or losing a higher-ordered structure in terms of proteins, from external causes, such as heat or radiation (LibreTexts, n.d).

Protein Misfolding & Prions

As described above, proteins fold so that they can perform their own specific function. But, sometimes protein folding might not go correctly. Events such as translational errors, genetic mutations, or incomplete formations might cause proteins to misfold (Fox et al., 2015). In many cases, misfolded proteins are very common and when they occur, proteolysis of these proteins occurs and they are broken down into their separate amino acid units (Ciechanover et al., 2015). Prions are intrinsically disordered isoforms of PrP(c), or the normal cell-surface glycoprotein (Jones, 2014). The reason prions are so dangerous is that they can be infectious in that they are transmissible through different methods and they also induce misfolding in proteins around them, which causes them to pile up in the brain and damage brain tissue.

Prion Diseases

Prion diseases are one of the four main branches of neurodegenerative diseases which are caused by prions. Prions are conformationally altered proteins that can clump up in the brain and cause other proteins around them to misfold, causing brain damage. Prions can affect animals and humans alike, causing similar symptoms in both (such as confusion). Prion diseases are quite fatal within a year and there are no cures for this type of disease.

Creutzfeldt-Jakob Disease

The main type of prion disease that affects humans is Creutzfeldt-Jakob Disease (CDC.gov, 2024). CJD itself can be described as "classic CJD" because there are other types of CJD: sporadic (sCJD), genetic (or familial), and acquired (variant CJD and iatrogenic CJD). Sporadic CJD is caused by a protein which spontaneously misfolds and causes other proteins to misfold as well. These misfolded proteins build up and damage the brain. Genetic CJD is caused due to family history; if someone in a family had CJD, the next generations are prone to contracting this disease. Finally, acquired CJD can be caused by contaminated factors in one's environment. Iatrogenic CJD (iCJD) is caused by things like contaminated neurosurgical instruments or contaminated human growth hormones, and on the other hand, variant CJD (vCJD) can be caused by meat contaminated by BSE and contaminated blood or blood plasma (CJD Foundation, n.d).

Possible Treatments for CJD

As of right now, there are scientists creating and carrying out studies that are trying to find possible treatments for CJD. One such study is testing the use of quinacrine as a possible treatment. Quinacrine was used in World War 2 to fight malaria (Bethesda, n.d). Quinacrine is a derivative of its predecessor, quinine (Yang et al., 2018). This is made from the bark of the Andean fever tree, otherwise known as a Cinchona tree (Walker et al., 2019). Quinacrine is still highly debated upon as an effective treatment for CJD because its mechanism of action is very unclear and indirect (Minikel, 2019). There is another possible treatment known as monoclonal antibodies. Monoclonal antibodies come in four types:

Murine: Synthesized from mouse proteins (ends in -omab)
Human: Synthesized fully from human proteins (ends in -umab)
Chimeric: Synthesized from part mouse proteins and part human proteins (ends in -ximab)
Humanized: Synthesized from small parts of mouse proteins and attached to human proteins (ends in -zumab)

Right now, these antibodies are used to treat many diseases, including neurodegenerative diseases, such as Alzheimer's. In this context of prion diseases, hypothetically, these antibodies could be used to block the original PrP(c) and therefore prevent a prion from being made (Mead et al., 2022). Unlike the mechanism of action of quinacrine, monoclonal antibodies are more direct and are seen to target these proteins. An antibody that has been tested is the PRN100 antibody. This antibody is actually synthesized from another named ICSM18. ICSM18 is an antibody that was seen in mice which was used to cure prion disease in them. ICSM18 was then humanized and is now named PRN100 (Minikel, 2019). In many studies, the PRN100 antibody has been shown to cure CJD from cultured cells in specific situations, but the situations are so specific that they do not apply to the real world. A study from the UCLH Clinical Facility in London involved treating six patients who had CJD with PRN100 and saw results that were promising.

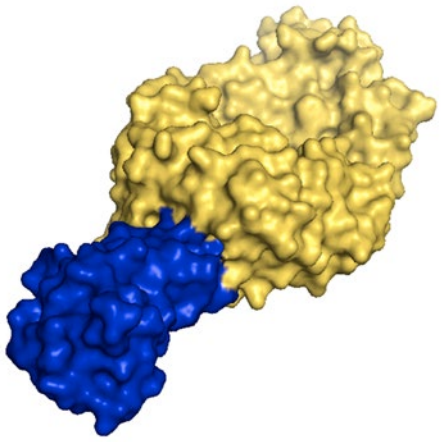

Figure 3. Figure representing the ICSM18 antibody (yellow) and the prion protein (blue). Source: Antonyuk, 2009. Description: As seen in the figure, antibodies have a more direct approach (they attach to prions), therefore they look more promising as a future treatment for Creutzfeldt-Jakob Disease and prion diseases in general.

Results & Discussion

The studies mentioned above have only been performed a couple times and with a small sample group, but they are steps in the right direction. Quinacrine was able to successfully get subjects to the 2-month mark, which is already a great deal. Monoclonal antibodies seem more successful than quinacrine as in the study from UCLH, the researchers saw that the patients were able to stay alive in a time period of 140 days; the only patient that had reached this date was a patient with iCJD (Mead, 2022). Through these studies, it is definitely shown that antibodies are more effective than quinacrine because though both got the patients to survive for an extended period of time, PRN100 is more direct and therefore allowed that study's patients to survive past 3 months. The reason that there are no treatments for prion diseases right now is because though prions follow many of the same characteristics of a virus, they are not a virus. They are misfolded proteins, which needs to be taken into consideration and many of the proposed solutions get wiped off the board because they are proteins. CJD can also be transmitted in many different ways: if one has the gene in their body, they might get genetic CJD; if one eats meat that is infected with BSE or CJD, they might get variant CJD; and etc. Taking these things into consideration is very vital, but it is clear that a solution is on the horizon for CJD.

Limitations

There are some limitations to this research paper. Firstly, this research paper was based primarily on data from other sources, so it might not be completely accurate. Second, Creutzfeldt-Jakob Disease is a disease that is not researched as much as other diseases, so there is not a lot of material to describe this disease with. This means that more research needs to be done not only on the disease itself, but its potential treatments as well. In addition, there are many different ideas on top of CJD; proteins, antibodies, medications, structures, cells, and more have to be discussed, and this paper did not have the right sources to describe all of these to the fullest extent. Finally, when discussing these treatments, it is difficult to consider the real-life applications of them and anything could happen based on who is administered either treatment. The only way to make this paper truly accurate from all perspectives would be to perform true experimentation and studies to see how these treatments are expressed in these situations (and not just have the paper discuss findings from other studies and research).

Conclusion

Prion diseases are some of the most dangerous diseases in the world because they very quickly destroy neural tissue as soon as the onset of the disease, which turns fatal. Almost all of the cases that include prion diseases in the world have been fatal within a year, which is what makes them so dangerous. Creutzfeldt-Jakob disease is one of these diseases and can be transmissible through a number of media, such as food, genes, and more.

This paper discussed not only the disease itself, but its proposed treatments that are going through experimentation and different studies. The mechanism of Creutzfeldt-Jakob Disease is prions. Prions are a type of protein that can cause other proteins around them to misfold. These prions then clump up in the brain and start damaging neural tissue. This mechanism is very similar to how viruses operate in the body, but the fundamental difference is that prions are proteins, not viruses.

Creutzfeldt-Jakob Disease is a disease that has not been researched much, but the research that is out there is about the composition of the disease itself and potential treatments. These potential treatments in these studies seem very promising but only more research and experimentation would solidify their legitimacy. A recommendation that could be taken into consideration is more research on possible treatments and more experimentation to find out the cause of sporadic CJD because finding anything (a pattern to the randomness) would be helpful in laying down the foundations to find the cure for CJD. If there is more research done in the future, then there may be a cure in the future which can finally end this dangerous disease for good.

Acknowledgments

I would first like to thank Dr. Jobin Varkey for educating and guiding me on this project. He has helped me learn more about neurodegenerative diseases and how they impact populations all across the world. Dr. Varkey has definitely made me more interested in not only science, but modern neuroscience and the leaps we have made regarding this subject which helps so many people today. He provided me with the groundwork to actually complete this research paper and helped me to discuss CJD with the utmost clarity and helped me take different perspectives into consideration. I would also like to thank Professor Virgel Torremocha for helping me smooth out my research paper. My paper would not have been this clear without Professor Virgel stepping in and improving upon my writing on this research paper in order to express my ideas and take different perspectives into consideration simultaneously. Finally, I would like to thank the institution of Gifted Gabber for providing me with an outlet to complete this paper with this much support and for educating me on neurodegenerative diseases.

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