Pharmaceutical and Non-Pharmaceutical Approaches to Managing Creutzfeldt-Jakob's Disease Symptoms

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Abstract

Human prion diseases are part of a family of rare neurodegenerative disorders, affecting 1-2 out of every million people globally. The most prevalent type of prion disease is Creutzfeldt-Jakob disease, also known as CJD. Due to the misfolding of a prion protein, there is rapid degeneration of the brain. These misfolded prions lead to the formation of colonies, destroying surrounding brain tissue, leading to inevitable fatality. As the disease progresses, symptoms continue to worsen, ultimately causing complete mobility loss, dementia, slurring of words, abnormal jerking movements, and more. The central issue with CJD is a lack of treatment options available. As of now, there is no cure, instead, therapeutic methods focus on providing relief to the patient. Exploring potential therapies for CJD patients is crucial, as a patient's physical and mental state is unpredictable throughout the journey with the disease. Furthermore, the rapidly progressing nature of the disease leaves little time for the trial of therapeutics, as it's extremely difficult to predict the timeline of the symptoms, and the symptoms require constant care and attention. Thus, it is necessary to find a manner in which symptoms can be managed as efficiently as possible, without disrupting the patient's comfort. This review summarizes a wide variety of pharmaceutical and non-pharmaceutical therapies for CJD patients, with the goal of highlighting therapies that best relieve patients of their symptoms. Ranging from the potential use of antibodies to acute rehabilitation, these studies explore methods that can help CJD patients live out the rest of their lives in the most satisfactory manner.

Introduction

Prion diseases, also known as transmissible spongiform encephalopathies, belong to a large family of devastating neurodegenerative conditions. Creuzfeldt's Jakob's disease (CJD) is the most prevalent type of prion disease, impacting people all over the world. In this disease, proteins in neurons are spontaneously converted into prions, a type of protein that triggers the misfolding of normal proteins, leading to their dysfunction. The formation of prions is exponential, causing significant damage to the patient's neurons (Cleveland Clinic, 2022).

Diagnosis of CJD is a tricky process, and oftentimes diagnosis occurs only after symptoms begin to appear. In fact, CJD can be contracted for many years with the patient being asymptomatic. However, the rapid degeneration only starts to occur after symptoms begin to show (Cleveland Clinic, 2022). There are three key ways to diagnose CJD. Electroencephalography (EEG), a type of test that records the electrical patterns of the brain to

find any irregularities, allows for the discovery of which stage of CJD the patient is currently in (Wieser et al., 2023). Findings such as diffuse slowing, a specific type of brain activity pattern, appear in EEG tests during early stages of CJD, as these are the first signs of cerebral dysfunction (Emmady and Anilkumar, 2023). Furthermore, magnetic resonance imaging (MRI), a non-invasive technique used to obtain detailed anatomical images, is a helpful strategy in the diagnosis of CJD, proving to be more than 90% accurate in diagnosis of CJD (Muacevic et al., 2020). Typically, abnormalities that display in CJD are found within the cerebral cortex or deep gray matter of the brain (Ranchod, 2023). Performing a lumbar puncture is also effective, as cerebrospinal fluid (CSF) is extracted from the spinal column and analyzed for prions (Prnp protein) (Johns Hopkins Medicine). Specifically, lab specialists are looking for the 14-3-3 protein, a marker for prion diseases such as CJD (Zerr et al., 1998). However, the only way to definitively confirm a diagnosis of CJD on a living patient is by performing a brain biopsy. In this procedure, a small portion of brain tissue is extracted and examined, but this process is considered a major risk to the patient (McPherson and DiNapoli, 2018).

There are four types of CJD: sporadic, familial, variant, and iatrogenic (NHS, 2021). Starting off with sporadic CJD, this is the most prevalent variant, comprising about 85% of all cases (CDC, 2022). There is no known cause for sporadic CJD, simply the fact that regular proteins in the brain spontaneously convert into prions, and this conversion persists indefinitely (NHS, 2022). Ninety percent of patients die within a year of symptoms onset, with the average duration of the disease being between 4-6 months (UCSF). Familial CJD is the result of a mutation in the Prnp gene, the gene responsible for making PrP proteins, which are known to be involved in cell signaling and neuronal homeostasis (True, 2017). This mutation displays an autosomal dominant inheritance pattern, meaning the closest relatives of an affected individual have a 50% chance of inheriting the pathogen. This variant of CJD accounts for about 10-15% of patients (UCSF, 2023). fCJD differs from sporadic CJD, as the disease course can vary from either a few months to over 5 years. Variant CJD is rooted from consuming infected cattle meat. The cow would have to have bovine spongiform encephalopathy (BSE - also known as mad cow's disease), which is similar to CJD, as it is also a prion disease. Prions convert into a pathogenic form that eventually damages the central nervous system of the cattle (CDC, 2021). However, there is an unclear timeline from infection to symptoms showing in cases of variant CJD. Finally, iatrogenic CJD spreads through the contamination of surgical equipment after the treatment of a CJD patient. This spread occurs due to lack of proper sterilization on surgical instruments before performing a procedure on the next patient (NHS, 2021). Though there are four variants to CJD, they all display a range of similar symptoms, including: memory loss, confusion, changes in behavior and personality, hallucinations, delusions, ataxia (problems with muscle coordination), balance issues, dystonia (muscle spasms and uncontrollable jerking movements), seizures, muscle atrophy (rapid loss of muscle mass and weight), and eventually, paralysis (Sitammagari, 2022).

Over the last decade, the presence of CJD in countries all over the world has increased, in some places more than in others. Studies have shown that there has been a rise in CJD

cases and CJD related deaths in countries such as Japan, the Czech Republic, Slovakia, the UK (Nishimura et al., 2020), and South Korea. In fact, researchers noticed a unique change in the increase of cases in South Korea, specifically that there was an “unusually high percentage” of CJD patients part of the 30-39 years age group, rounding to about 1% of total cases in South Korea (Kim and Jeong, 2022). Though many of the listed countries noticed an increase in sporadic CJD cases, the UK had a dramatic rise in the number of variant CJD cases, a rarer type of the disease. As of spring 2022, the UK has become the country with the current most active variant CJD cases, topping at 175 cases. France and Ireland follow the UK, but are nowhere near the number of active vCJD cases that the UK contains (The University of Edinburgh, 2022). It is unclear the cause of this global increase in cases, and whether it indicates increased prevalence of CJD or an increase in detection.

Pharmaceutical approaches to treating CJD

Antibodies

Antibodies have been proposed as a potential therapy to help a patient’s body fight foreign prion proteins. Typically, antibodies are proteins that are naturally produced and serve to help the immune system fight foreign substances, known as antigens, such as infections, allergens, and toxins. They are produced by white blood cells (WBC) and the structure of each antibody slightly differs. It is a Y-shaped molecule, however each tip has a unique amino acid sequence required to fight the antigen. When an antigen comes in contact with a WBC, the WBC divides and multiplies to release millions of antibodies into the bloodstream. The treatment for CJD differs though, as it is a clinically created antibody (in a lab setting), known as a monoclonal antibody, rather than a naturally produced antibody from the human immune system. Monoclonal antibodies are created to target a specific antigen, classifying them as a type of immunotherapy for diagnoses such as cancer, rheumatoid arthritis, heart disease, lupus, multiple sclerosis, and more (Cleveland Clinic, 2022). Prior knowledge about antibodies has led to the creation and clinical trial of PRN100, a monoclonal antibody designed to prevent prions (PrPC protein) from continuing to multiply by destroying them. In a study conducted by University College London (UCL) researchers, PRN100 was offered to 6 CJD patients, who were not in the terminal stage of the disease. The PRN100 was given intravenously in small increments every 2 days, and eventually larger increments every 2 weeks, if negative effects were not recorded. According to the results, this monoclonal antibody method was safe to use and successfully reached encouraging CSF and brain tissue concentrations that were noted in patient autopsies. In fact, the use of PRN100 led to the longest clinical duration of iatrogenic CJD ever recorded. Though death still occurred, there were no clinically adverse effects seen,

giving hope for the use of PRN100 in the future, if its success continues to be seen with more extensive testing (Mead et al., 2022).

Antisense Oligonucleotides

The use of antisense oligonucleotides (ASOs) is a potential therapy for CJD utilized prior to the formation of prions, targeting these proteins at the level of their transcripts. ASOs bind to specific RNA sequences to control the production and expression of their respective proteins. These sequences, generally 15-20 nucleotides in length, target complementary RNA, with the Watson and Crick base pairing rules. Though ASOs have been in practice for the last few decades, new modifications have been explored for increased stability, efficiency, and response. Typically, ASOs function either through RNA cleavage or RNA blockage. Within RNA cleavage, there are two main methods. To begin, there is RNase mediated degradation, in which a complex is formed between the ASO and its complementary RNA. This complex acts as a substrate for the enzyme RNase, which has the key role of degrading RNA from the ASO-RNA complex, essentially blocking the formation of the protein. The second method is known as RNA interference, where small interfering RNAs (siRNAs - 22 nucleotide double stranded RNA sequences) interact with an enzyme known as the Argonaute 2 enzyme, to form an RNA induced silencing complex (RISC). RISC then degrades the passenger strand of the siRNA, and the remaining strand guides RISC towards the complementary mRNA. The enzyme Argonaute 2 will then cleave this mRNA and silence its expression. Moving onto RNA blockage techniques, there is steric hindrance, which is the slowing of a molecule's efficiency due to its bulk. These ASOs bind to the target RNA sequence and prevent their assembly with a ribosomal subunit, inhibiting translation. These ASOs have a very high binding affinity for their target RNA strand. Finally, there is splice modulation, a technique used to address alternative splicing and frameshift mutations that alter pre-mRNA splicing patterns. ASOs can either bind to the pre-mRNA transcripts to fix the reading frame and produce a functional protein, or they can bind to the pre-mRNA to prevent the transcript sites from being accessed (Dhuri et al., 2020).

ASOs can play a role in the formation and inhibition of proteins, which leads to the discussion of how they can be used to treat prion diseases. In a 2019 study, researchers worked on the use of ASOs and how they can extend the survival of mice infected with prions. ASOs that were complementary to the endogenous prion mRNA were screened and the researchers came up with ASO1 and ASO2 as two potential therapeutics. The primary difference between ASO1 and ASO2 is how they target different regions of the PrnP gene (the 3′ UTR and intron 2, respectively). For preliminary results, both ASOs were dosed in the brain and spinal cord of uninfected wild-type (WT) mice and there was a significant reduction of Prnp mRNA noted in the ipsilateral entorhinal cortex, hippocampus, and thoracic spinal cord, in comparison to mice treated with saline. Next, mice were infected with an established prion disease similar to that of CJD. These mice were injected with ASO1 about 15 days before the expected onset of symptoms. The results show that the use of active ASO1 delayed the onset of symptoms by

33% and the clinical phase of the disease lasted 3x longer than the mice treated with saline. Overall, the survival time of treated mice increased by 55%. This study highlights the successful delivery of ASOs to the brain through the spinal cord in mice, achieving similar brain distribution as spinal injections in primates. This sheds possible light into dosing humans with ASOs through a lumbar puncture, which is already utilized as a CJD diagnosis technique (Raymond et al., 2019).

Drugs

Though researchers have not found drugs to target prion proteins specifically yet, drugs have been implemented to manage common CJD symptoms. Benzodiazepines are a family of depressant drugs used to slow down signals between the brain and body. Though benzodiazepines can be used to relieve anxiety, insomnia, and even alcohol withdrawals, they can also be used to treat brain related issues such as seizures (ADF, 2023). Specifically, clobazam, a long-acting benzodiazepine, has been used in treating CJD related seizures. Clobazam increases the permeability of chloride ions through neuronal cells, by increasing the frequency of ligand gated ion channel openings. The increased cell potential as a result activates GABA, an inhibitory neurotransmitter. As a result, there is a decrease in neuronal activity and excitability as a whole in the cell, stopping the specific signals that cause seizures (Maille et al., 2023). A study found that initiation of clobazam along with levetiracetam and lacosamide (Liu et al., 2023), two supporting anti-epileptic drugs, led to a significant decrease in seizures in CJD patients, stopping them all together within 72 hours. Researchers suggest that benzodiazepine receptors remain intact in CJD patients, allowing them to be effective in helping patients (Maille et al., 2023).

Furthermore, sodium valproate has also been used to reduce seizures, by controlling excessive electrical activity in the brain. Sodium valproate can achieve this by blocking certain voltage gated ion channels to reduce the high frequency transmission of neurons (Rahman and Nguyen, 2022). This is a type of slow release medicine, typically taken in the form of a tablet (NHS, 2021).

Finally, flupirtine maleate (FLU) is a non-opioid pain relieving drug, which functions by blocking the glutamate N-methyl-D-aspartate receptor (Harish et al., 2012), a primary excitatory neurotransmitter receptor in humans (Jewett, B and Thapa, B., 2022). In previous cell culture experiments, FLU was able to prevent apoptotic cell death of neurons that were previously treated with parts of prion proteins. Because of this, FLU was implemented in a study with CJD patients, and the results seemed promising. CJD patients treated with FLU showed significantly less deterioration when periodically tested for dementia under the Alzheimer's Disease Assessment Scale. Though further studies are necessary to determine whether FLU could be part of a stable CJD treatment plan, it has had positive effects on cognitive function of these CJD patients; there is great hope for its potential (Otto et al., 2004).

Non-pharmaceutical methods

Pharmaceutical methods have the capability to help CJD patients with their symptoms, however in some cases, the progression of the disease can be too quick for the implementation of these methods. For this reason, non-pharmaceutical methods can be key in managing the less complex symptoms, providing quick comfort to patients.

Visual art therapy

Visual art therapy consists of the use of creative techniques to allow patients to express themselves, in an artist's manner. Through art, patients' psychological and emotional undertones can be analyzed, making it a great way for therapists to dig deeper into a client's life. Therapists are trained to draw connections between the patients' artistic choices and what is occurring within their life in order to help them. Scientifically, art work has proven to reawaken memories and reveal stories, and display unconscious thoughts (Psychology Today, 2022). In relation to CJD, art therapy can be useful in increasing patient awareness of what is going on, along with evoking spontaneous expression of emotion. As the disease progresses, there are obvious physical challenges, but there are a great deal of mental challenges as well. The effects of art therapy on CJD was tested in a case study, where the key subject was Ms. A, a middle-aged woman with disease progression in its early stages. For 23 weeks, she participated in weekly art therapy sessions, with the goal being to increase her comfort with the circumstances of her disease. The researchers noticed that art therapy provided her with short windows of time where she was able to deeply express her feelings about what was happening to her. This showed that despite rapid changes in her brain and the continuous decline in her physical capabilities, she was still aware of her surroundings. In fact, art therapy created a safe environment for Ms. A, where she could feel less overwhelmed and anxious by the reality of the disease (Shrestha et al., 2016). As shown in this case study, visual art therapy has the potential to calm the minds of CJD patients, creating a calmer and safer environment for them as the disease progresses.

Acute Rehabilitation

Acute rehabilitation is a type of care where a patient receives whatever medical attention they may require, whether its constant medication or the monitoring of the progress of a disease, at the same time as some sort of physical therapy (Santé, 2016). This can prove to be quite beneficial to patients with CJD, as analyzed in a case study from 2022. A 62-year old man, after a recent diagnosis of CJD entered a 14 day acute rehabilitation program, in hopes to improve his mobility. During this two week study, the patient underwent a series of treatments, including therapeutic exercise, gait training, neuromuscular reeducation, cognitive behavioral

therapy, and voice therapy (Copeland et al., 2022). The main purpose of therapeutic exercise is to correct any impairments to the anatomy and restore skeletal/muscular function (Bielecki and Tadi, 2023), whereas gait training focuses on improving the ability to walk (Eng and Tang, 2007). Neuromuscular reeducation worked to restore normal function of his nerves and as a result, muscular function (AmeriHealth, 2018). Throughout the process, he was also treated with midodrine to manage orthostatic hypotension, to keep his standing blood pressure levels normal (Prescr, 2021). The results were quite promising, as by the time of his discharge, the patient was able to complete daily activities with minor assistance. At the beginning of the 2 weeks, he required moderate assistance, around 50% caregiver effort and 50% of his own effort. However after 2 weeks, it shifted to 75% patient effort and only 25% caregiver effort for day-to-day tasks. Though this was just a case study, acute rehab could be a promising therapy to improve the mobility of CJD patients (Copeland et al., 2022).

Discussion

CJD is the most prevalent type of prion disease, which is truly a tragedy considering its rapidly progressing nature and the lack of consistent treatment options available (John Medicine Hopkins). However, there are therapies, both pharmaceutical and non-pharmaceutical that can be implemented to help alleviate symptoms, to hopefully lead to a more comfortable journey with the disease. From the trial of monoclonal antibodies that destroy prions in the body, to the successful implementation of ASOs to target prions before they are even formed, and finally, the use of clinically-approved drugs such as clobazam, sodium valproate, and flupirtine maleate to control seizures and dementia, these pharmaceutical methods demonstrate heavy potential for attacking CJD from a molecular perspective. Through further experimentation with these proposed solutions, there is much hope for solving the mystery behind CJD.

On the other hand, non-pharmaceutical approaches can be an easier method of providing relief to patients, without partaking in any complicated processes. However, there is a key issue with the direction that CJD research has fallen under. Rather than targeting the root of the issue, which is the spontaneous multiplication of prions, research has been focused on addressing symptoms of the disease. This can prove to be useful in the short term, but as the prevalence of the disease increases, there is a greater need for finding a reliable solution to CJD, in order to save lives. As mentioned above, there has been a rise in CJD related death rates in the following countries: Japan, the Czech Republic, Slovakia, the UK (Nishimura et al., 2020), and South Korea (Kim and Jeong, 2022). Again, the reason for this growth in cases is unknown, however it's hypothesized to partially be due to heightened awareness of CJD and the advancement of diagnostic technology over time.

Overall, there is a desperate need for more research in the prion-disease field of neuroscience, as the lack of knowledge about the disease is a problem in itself. There are still many unanswered questions, making it extremely difficult to design a solution to control the disease. Without concrete answers on the basics of CJD, such as how prions initially form, there

is no way to combat the disease once and for all. However, CJD is similar in nature to other neurodegenerative diseases, in terms of being caused by the misfolding of proteins that ultimately lead to neuron loss (Lamptey et al., 2022). For example, Alzehmier's disease is caused by the build-up of the misfolded amyloid-B protein (due to mutation) in neuronal cells (Ashraf, 2014). A common Alzheimer's treatment utilizes cholinesterase inhibitors, which are a group of drugs that block the breakdown of acetylcholine into acetate and choline. As a result, there's an accumulation of acetylcholine, which continues to activate receptors to regulate functions of the nervous system, improving overall dementia. This could prove to be useful in reducing CJD related dementia, however there is no way to truly determine its effectiveness without further experimentation (Sadiq, 2023). Parkison's disease has similar symptoms to CJD, as it is also a brain disorder that causes uncontrollable movements and difficulty with balance, coordination, and even walking and talking as the disease progresses. Accumulation of a misfolded form of the alpha-synuclein protein leads to the formation of toxic clumps, which ultimately lead to cell death (Cure Parkinson's). Deep brain stimulation is a treatment recommended to Parkinson's patients that don't respond well to medication, where electrodes stimulate specific areas of the brain that are involved in movement, to stop symptoms such as tremors, slowness in movement, and rigidity. Again, DBS has never been tested on CJD patients, and there's no research to demonstrate the reactions of prions to it, however, the similarities in causes and symptoms of CJD and Parkinson's make the future use of DBS in CJD an appealing option (NIA, 2022).

To summarize, there are still ways to go in order to find a cure that is reliable across a wide variety of CJD cases and that targets the root cause of the disease. The lack of research in the field is the biggest obstacle in the journey to discovering how to end CJD once and for all.

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