Huntington's Disease: A Comprehensive Overview on the Pathophysiology, Diagnosis, and Treatment

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Abstract

Huntington's Disease is a rare neurodegenerative disease that results in nerve cell damage, causing difficulty in performing motor movements. The pathophysiology of HD is very nuanced and unique, as it involves a specific type of mutation in the Huntingtin Protein. This paper will focus on the mechanisms, diagnosis, and treatment of Huntington's Disease (HD). It will delve into the basics of genetic diseases, covering topics such as DNA replication and repair, genetic mutations, and an introduction to HD. Then there will be an extensive review of the pathophysiology of HD, going over trinucleotide repeats/expansions, the relation between the number of repeats and the age of onset and severity of the symptoms that a patient with HD presents, and the way in which processes such as autophagy and mitochondrial function get impacted as a result of HD. Furthermore, the diagnosis of HD will also be discussed, going into the challenges of diagnosis, differential diagnosis, and methods to test for Huntington's Disease. Along with diagnosis, prognosis will also be mentioned, where the paper will delve into the long-term outlook of HD in terms of survival rates, the number of cases of HD, and the overall course of the disease. As HD is a very rare genetic disorder, it has no cure and a 0% survival rate. Therefore, a key aspect of this paper is the focus on the future of HD treatment, where numerous ongoing treatment implementations will be discussed and extensively analyzed in order to determine the most effective treatments for HD.

1. Background

Genetics involves the study of genes, heredity, and variations. In some cases, mutations, or changes in the genome, can cause genetic diseases with diverse impacts on human health. There are two types of mutations: inherited, or germline, and somatic mutations. Germline mutations are inherited by offspring from their parents. It's important to note that inheriting a mutation does not necessarily mean that an offspring will inherit the disease. Mutations are associated with different degrees of penetrance that determine the likelihood of a particular genotype impacting a phenotype. On the other hand, somatic mutations occur in somatic cells, which are non-reproductive cells.[1] Somatic mutations are mutations that occur in somatic, or body, tissues. They can occur anytime throughout an organism's lifetime.[2] While not inherited, somatic mutations can still cause diseases such as cancer and neurodegenerative diseases. Somatic mutations include insertions, deletions, and base substitutions.[1]

Repeat expansion mutations are a type of somatic mutation that occur when a specific DNA sequence is repeated. When repeat expansions occur in somatic cells, they can generate diseases, especially neurodegenerative diseases. An individual can inherit a certain number of repeats from their parents. However, repeat expansion mutations can also expand in somatic cells throughout an individual's lifetime, increasing the number of repeats. The number of the repeats may dictate the severity of a disease. Huntington's disease (HD) is an example of a neurodegenerative disease caused by expansions of a trinucleotide repeat.[3] This paper will explore the role of repeat expansion mutations in Huntington's disease pathogenesis and explore new approaches to treating this incurable and deleterious disease.

2. Fundamentals of Huntington's Disease

HD is an autosomal dominant disease caused by somatic expansions in the Huntingtin (HTT) protein, a key mediator of DNA damage repair. Cytosine-adenine-guanine (CAG) trinucleotide repeats are mutations associated with HD.[4] Most patients are heterozygous for HD.[5] Offspring with at least one affected parent have a 50% chance of inheriting the disease. [1] Currently, there is no cure for HD, and available treatments are limited. Furthermore, the survival rate for patients with HD is 0%. Hence, there is an urgent unmet need to identify novel treatments or cures for patients with HD.[6]

Mutational Mechanisms

The mechanisms by which mutations arise and the cell's method of fixing them involve the processes of DNA replication and repair. DNA replication is the process of copying DNA during cell division. DNA replication consists of three phases: initiation, unwinding, and elongation. Many enzymes, such as helicase, primase, polymerase, topoisomerase, ligase, and single-stranded binding proteins, contribute to this process. All of these enzymes coordinate to ensure the successful replication of DNA.[7]

DNA replication is an error-prone process. The DNA damage repair pathway ensures that any mutation that occurs during DNA replication is repaired. If the mutation occurs in germ cells, it can be inherited by offspring of the individual and is known as a germline mutation. If the mutation arises in a somatic cell, it can be passed down to daughter cells within the same individual through mitosis. The process of repairing DNA damage by removing the damaged base and replacing it with a new base is called base excision repair (BER). [8] The removal of the base is done through a specific DNA glycosylase.[9] It's also involved in maintaining economic stability and preventing neurodegenerative diseases. [8] BER typically works with fixing damage that occurred due to processes such as oxidation and alkylation. [9] Another mechanism of DNA

repair known as nucleotide-excision repair (NER) removes larger DNA lesions. NER can recognize and efficiently correct a variety of different types of mutations. However, if these mutations are missed, they can lead to genetic diseases. [7]

The Role of HTT in DNA Repair

Trinucleotide expansions are the cause of HD. These expansions occur in the Huntingtin protein (HTT), giving rise to mutant Huntingtin (mHTT). Expansion can occur due to oxidative DNA damage, which accumulates with age. Expansions may also be caused by 8-dihydro-8-oxoguanine DNA glycosylase, an enzyme in the base excision repair pathway in DNA repair. If the DNA repair fails, then insertions and deletions can occur in the genome. Genome association studies have identified genes linked to HD that are involved in DNA damage repair. [10]

The inhibition of DNA repair in postmitotic neurons can cause an accumulation of DNA lesions. In HD, impaired function of the HTT protein can further promote the accumulation of mutations due to impaired DNA damage repair. The functions of HTT include sensing reactive oxygen species (ROS) that can cause DNA damage, identifying DNA lesions during transcription, and facilitating DNA repair by acting as a scaffold to organize the transcriptional repair complex. Huntingtin also helps identify lesions and facilitate DNA repair during transcription, as it also localizes to the transcription repair complex. Mutations in HTT impair the function of the TCR complex, leading to unrepaired DNA damage and ATM hyperactivation[10]. If left unrepaired, DNA damage can cause mutations, mitochondrial dysfunction, defects in vesicle trafficking, protein misfolding, and cell death.[3]

Symptoms

HD is a movement disorder. The symptoms of HD can be divided into two categories: movement defects and cognitive dysfunction. Typically, hyperkinetic movements in HD patients will start occurring early after disease onset before becoming more prominent. [11] HD may also be associated with motor impersistence. Patients may exhibit abnormal eye/tongue movements, tics, milkmaid's grip (weak grip), an inability to maintain gaze, and myoclonus, or abrupt twitching. Furthermore, gait and postural stability, as well as saccadic (discontinuous) function, become impaired. HD patients can also experience mild forms of oculomotor apraxia (inability to move one's eyes in a vertical, horizontal, and/or lateral motion). When individuals are asked to turn to one side, they turn their head first, and then slowly move their eyes to that same side. The presence of these symptoms can lead to a diagnosis of HD. The Luria tri-step is a test performed by doctors in the clinical diagnosis of HD. During this test, patients are asked to

perform a repetitive sequence of making a fist, then placing the medial side of the hand down, and then the palm. Patients who struggle doing so may have an underlying neurological issue, suggesting a potential diagnosis of neurodegenerative diseases such as HD. [11]

People with HD experience cognitive dysfunction as well. These behavioral issues change throughout the stages of HD. The early stages of HD often involve loss of mental flexibility, difficulty with memory (especially of retrieval), and attention/concentration defects. As the disease progresses, patients develop forgetfulness, bradyphrenia (slowness of thought processes), impaired visuospatial abilities and ability to manipulate knowledge, reduced syntactic complexity, and speech problems. Individuals with HD may also exhibit schizophrenic psychoses (such as paranoia delusions), as well as explosive and aggressive outbursts, apathy, alcohol abuse, sexual dysfunction, and increased appetite delay. [12]

Onset and Progression of HD

Onset describes that time when the symptoms of a disease first appear. The number of trinucleotide repeats in a patient's genome correlates with severity of HD and inversely correlates with the age of disease onset.[3] In a healthy individual, the HTT protein will have around 36 repeats. HD with disease penetrance occurs when the HTT protein has 36-39 repeats. Patients with 40 or more repeats in HTT display more severe symptoms and a decreased age of onset. Majority of HD patients have onset during their adulthood. [13] Juvenile onset occurs very rarely in HD patients.[14]

Patients with early onset HD typically show more behavioral symptoms such as anxiety, depression, demotivation, irritability, obsessive-compulsive behaviors, and drug abuse. Furthermore, they present depression and irritability. During the advanced stages of disease, their symptoms become severe again. [15] HD is also associated with seizures in approximately 30%-50% of patients with HD onset before age 10. Furthermore, in juvenile onset, patients undergo rapid and severe cognitive deterioration associated with speech and language delay. [11]

The symptoms of adult onset HD progress in several distinct phases. The early states of HD onset in adult patients involve the loss of mental flexibility, executive dysfunction, memory difficulties (especially of retrieval), and attention defects. As the disease progresses, patients develop forgetfulness, bradyphrenia (slowness of thought processes), impaired visuospatial abilities, reduced syntactic complexity, cortical speech problems, reduced word finding and paraphasic errors. Adult patients with HD may also exhibit affective or schizophrenic psychoses, as well as explosive and aggressive outbursts, apathy, alcohol abuse, sexual dysfunction and increased appetite. In terms of psychopathology, people experience early personality changes,

depression, hostility, obsessive–compulsive symptoms, anxiety, and heightened interpersonal sensitivity.[11] Neuronal degeneration in the basal ganglia has been linked to memory impairment, slurred speech, chorea, weight loss, and personality changes.[16]

As mentioned earlier, people with HD continue to experience severe symptoms until they eventually pass away. Typically, people with HD die after having had it for 15-20yrs.[6] The final stages of HD consist of difficulty with performing daily tasks and being able to move.[17] Most HD patients die as a result of the disease itself. However, an alternative cause of death for HD patients include suicide.[18] Another cause of death is with respiratory infections such as aspiration pneumonia. The pneumonia was discovered through a study analyzing the death of HD patients from the Leiden University Medical Center in the Netherlands. [19]

Accelerated Aging in HD

The brains of patients with HD show signs of accelerated aging. Telomeres, which are the ends of chromosomes that protect the DNA from damage during replication, shorten with age. For this reason, aging is linked to shortened telomeres. Several neurodegenerative diseases are characterized by shortened telomeres in leukocytes. In patients with HD, leukocytes exhibit shortened telomeres compared to control individuals, suggesting that there is correlation between accelerated aging and HD. Epigenetic alterations are also associated with accelerated aging. In the brains of HD patients, accelerated epigenetic aging has been observed in the striatum, a region of the brain involved in controlling body movement. [5] The striatum is also the part of the brain most affected by HD. Accelerated brain epigenetic aging has also been observed in other neurological disorders such as Alzheimer's disease, Down syndrome, and HIV-associated neurocognitive disorders.[20] It is important to keep this information in mind when thinking of treatment options for HD as it's pertinent to neurological disorders. Finding a method of combating accelerated aging can be beneficial for developing a cure for HD and other neurological disorders in general.

Differential Diagnosis

Because HD is such a rare condition, it is often difficult to diagnose. Additionally, the symptoms of HD overlap with many other neurological disorders, and it may be challenging for clinicians to differentiate HD from other diseases. If someone presents with the symptoms associated with HD, then HD will most likely not be the first diagnosis that is presented by a physician.[11] In this section we will explore some of the differential diagnoses for HD.

Chorea-Acanthocytosis

An example of differential diagnosis for HD is chorea-acanthocytosis, a disorder that causes involuntary movement. Chorea-acanthocytosis is characterized by fractioned saccades and square-wave jerks (involuntary, horizontal movements that interrupt fixation). At onset, memory impairment, dysexecutive problems and schizophreniform occur. This disorder also presents with apathy, depression, bradyphrenia, and obsessive-compulsiveness. [12]

Ataxia

Ataxia is a cerebellar atrophy typically found in juvenile HD. While ataxia is a differential diagnosis of HD, it can also be a symptom present in HD. The most common type of ataxia is Friedreich ataxia, where some symptoms consist of progressive trunk and limb ataxia, slower lower limb reflexes, Babinski sign, dysarthria, visual problems, scoliosis, and cardiomyopathy. Ataxia can cause another disorder called Gait Disorder. Gait refers to a pattern of movement used when walking/running. Gait examination is helpful when identifying HD-like syndromes. [12] Out of all of these HD-like syndromes, gait and chorea appear to be the most common disorders when it comes to differential diagnosis. Because they are common disorders, people who have HD might get misdiagnosed due to these commonalities and the fact that HD is not a common diagnosis. [12]

3. Pathophysiology of HD

As the CAG sequence in the HTT protein expands, or duplicates, it forms a polyglutamine (polyQ) stretch, a consecutive set of repeated codons encoding the amino acid glutamine (Q). PolyQ expansions can alter the structure of HTT protein, leading to misfolding and aggregation of mHTT. Before going into detail about misfolding, it is important to understand the process of normal protein folding. [13]

Process of Protein Folding

The native conformation of a protein is the conformation with the lowest amount of free energy, making it thermodynamically stable. In order to reach this state, the protein undergoes numerous sporadic fluctuations of the polypeptide chain as a result of Brownian motion. This allows the amino acids in the polypeptide chain to interact with each other in different conformations. The amino acids interact until the polypeptide chain is able to find the lowest energy conformation. The folding process of a protein starts with the formation of a folding nucleus. After the nucleus is formed, the entire surrounding structure of the polypeptide chain

condenses, allowing the formation of disulfide bonds between neighboring cysteine residues. The formation of secondary structure contributes to the native state conformation and protein stability. Chaperone proteins bind to the protein in order to promote protein folding in ao a stable conformation and prevent misfolding arising from suboptimal interactions within and between polypeptides.[13]

Protein Misfolding and its Impact on HD

When a gene is mutated, the protein it produces may have an altered structure and function, leading to the formation of aggregates that are difficult for the cell to remove through normal proteostatic mechanisms, resulting in cell damage and death. Protein misfolding can occur due to somatic mutations in the gene sequence, errors in transcription or translation, or failure of chaperone protein to prevent misfolding. When a protein misfolds, the function of the protein is impaired, causing hydrophobic residues to face towards the outside of the protein. Since the inside of a cell is aqueous, the protein attempts to stick to another protein in order to cover the exposed area. The exposed parts are able to form bonds with other misfolded proteins, allowing the misfolded proteins to stick to one another. These aggregates can form large structures: oligomers, protofibrils, and fibrils.[21] Aggregates may impact numerous cellular functions in the body, including the function of neuronal cells, leading to neurodegeneration. In this way, the accumulation of protein aggregates is thought to cause the numerous neuropsychiatric symptoms associated with HD.[11]

Pathogenic Mechanisms of Trinucleotide Expansion

As mentioned previously, HD is caused by trinucleotide expansions, more specifically, CAG expansions, in the *HTT* gene. These expansions form polyglutamine tracts. The expanded polyglutamine proteins impact vesicle trafficking, lipid metabolism, mitochondrial dysfunction, autophagy, and transcription and are thought to drive the pathogenesis of HD. [22]

Mitochondrial Dysfunction

Mitochondrial dysfunction may play a role in HD pathogenesis. Misfolded protein aggregates, such as amyloid beta, which is also thought to be involved in Alzheimer's disease, interact with cell membranes and phospholipid bilayers. Binding of misfolded proteins to membranes may cause membrane or membrane-bound proteins instability and dysfunction , potentially causing the formation of “leaky” pores in the membrane. Induced pore formation results in an increase in intracellular ion concentration, specifically, Ca^{2+} .[13] The increase in

concentration of Ca^{2+} in the mitochondrial matrix leads to decreased ATP levels, which may enhance ROS production. Increased ROS can damage mitochondrial DNA, causing changins in the mitochondrial proteomes, which leads to mitochondrial dysfunction in individuals with HD.[23] Furthermore, mitochondrial dysfunction can also occur due to DNA damage. mtDNA can become damaged due to errors during DNA replication. ROS may also exert harmful effects on mtDNA. For example, ROS can cause DNA strand breaks, base modification or deletion, and cross linking, all which alter the structure and function of mtDNA, potentially impairing mitochondrial function.[24]

Autophagy in HD

mHTT influences membrane trafficking, lysosomal biogenesis, and autophagy, the waste management system of the cell. Autophagy is a cellular process that requires endosomes, peroxisomes, and lysosomes in order to remove damaged material from the cell.[3] The mechanisms by which autophagy occurs involves a phagophore, which is an isolation membrane. The phagophore engulfs the waste material from the cell, becoming an autophagosome. The autophagosome then fuses with the lysosome. The waste is then transported outside to the cytoplasm where it can be used to build macromolecules. [1]An imbalance or alteration in lipid metabolism may affect organelle integrity and influence the phenotypes associated with HD.[3] Studies with drosophila and mice suggest that HTT impacted autophagy. A study by Zeithlin and colleagues found that the removal of a polyQ domain from HTT resulted in an increase in autophagy in neurons. Later research identified the domain of HTT that mediates HTT interaction with proteins involved with autophagy. These findings suggest that autophagy may impact the pathogenesis of HD through mechanisms that remain incompletely described. [22] Because autophagy degrades protein aggregates, drugs that increase autophagic flux could potentially be used to treat HD. Experiments in mammalian cells suggest that drugs that induce autophagy may decrease phenotypes associated with HD in human patients. An example of one such treatment is rapamycin, an mTOR inhibitor. mTOR is a protein kinase responsible for cell regulation and growth. mTOR is also known to inhibit autophagy, making it a potential option for treating HD. [25] Studies suggest that rapamycin improved neurodegeneration and symptoms in animal models of HD for mice and flies. [5] Scientists insert a human genomic fragment which encodes HTT into the mice. The genomic fragment contains a CAG expansion, resulting in these species obtaining HD. Through this set up, scientists were able to appropriately test the impacts of rapamycin in HD. [26]

4. Potential HD Treatments

Currently, there is no cure for HD. [6] However, scientists are working to develop therapies for patients with HD. In this section we will review some potential therapeutic options for HD.

What's Currently Being Used?

Pharmaceutical products including the dopamine receptor blockers tiapride, haloperidol, fluphenazine, olanzapine and risperidone, have been shown to reduce comorbid psychiatric symptoms and chorea in HD. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors have been thought to help HD patients with reducing depression and anxiety levels. [27]

AAVs

Scientists have developed several potential systems to deliver treatments, such as adeno-associated viruses (AAVs). AAVs are viral vectors, viruses that have been engineered to deliver specific sequences of DNA. Prior studies suggest that AAVs are safe for use in humans.[27] AAVs have many advantages: they have multiple stereotypes, are nonpathogenic, and don't integrate into the genome. However, AAVs also come with disadvantages. AAVs can induce immune responses due to the body rejecting the virus. [28] The efficacy of AAV-miRNAs targeting mHTT has been examined using in vivo models. [27] Currently, miRNA treatments have become very popular amongst scientists in treating diseases. Mature forms of miRNA have been commonly synthesized to deliver into damaged cells or tissues. Modified miRNAs have been developed to prevent RNase attacks. Phosphorothioate (PS) RNA is generated through using sulfur in the phosphodiester bonds of the RNAs in order to decrease the attacks of RNase. [27]

In a mouse model of HD, scientists used an AAV serotype-5 vector to deliver the anti-mHTT miRNA into the mouse.[28] Additionally, the company Uniquire is currently developing a gene therapy for HD using AAV5 called AMT-130 therapy. AMT-130 therapy delivers AAV5 to the brain parenchyma through MRI guided injections, potentially reducing the expression of mHTT. AMT-130 therapy is currently being tested for safety and efficacy in a Phase I/II clinical trial.[28]

Stem Cell Replacement Therapy

Stem cell replacement therapy is another potential HD treatment that involves transplanting stem cells into the brain. These stem cells have the ability to develop into normal brain cells that can replace lost neuronal cells.[3] Stem cell replacement therapy has been tested using rodent models of HD and administered mesenchymal or dental pulp stem cells. However,

a challenge to this form of therapy is graft failure due to the body mounting an immune response against the transferred stem cells.[27]

Cellavita is a potential stem cell therapy treatment that involves the transplant of dental-pulp-derived mesenchymal stem cells (DMSCs).[16] DMSC transfer can increase tissue regeneration. Their effect on tissue regeneration is controlled by their secreted substances like extracellular vesicles.[29] These cells can be collected and cultured, allowing the tissue to rapidly develop. [30] A study found that the administration of stem cells in HD increased brain-derived neurotrophic factor (a protein that protects nerve cells) levels in the striatum and cortex, resulting in enhanced neuroprotection. DMSCs can differentiate into neuronal cells, allowing tissue regeneration to be effective in HD treatments.[16] Furthermore, “Clinical Extension Study for Assessing the Safety and Efficacy of the Intravenous Administration of Cellavita-HD in Huntington's Disease Patients Who Participated in the ADORE-DH Study” (clinical trial number NCT04219241) is a phase 3 clinical trial studying the safety and efficacy of Cellavita in HD patients. The trial started in February 2020 and was completed in 2022.

CRISPR/CAS9

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a type of technology utilized to modify DNA in organisms by cleaving and replacing a specific DNA sequence. [31] CRISPR consists of two main components. These two components are a guide RNA and CRISPR-associated protein 9 (Cas9). Cas9 is used to cut the specific section of DNA that needs to be modified. The guide RNA directs the Cas9 to this particular location. [32]

CRISPR has been used to treat cardiovascular disorders and hematological diseases.[31] CRISPR technology has also been proposed as a treatment option for HD, as it can be used for the selective deletion of mHTT repeats. [23] CRISPR may represent a promising therapeutic option for patients with HD in the near future. However, there have been some issues with using CRISPR for HD (and other neurodegenerative diseases) because CRISPR cannot work in non-dividing cells. This is because homology directed repair required for CRISPR-induced genome editing does not work in non-dividing cells. [31]

Clinical Trials with HD

Currently, there are numerous ongoing clinical trials aimed towards developing drugs for HD treatment.

Metformin

"Testing METformin against cognitive decline in HD" (clinical trial number NCT04826692) is a phase 3 trial testing the efficacy and safety of metformin in HD. Trial NCT04826692 started in December of 2021 and is estimated to end August 2024. [33] Metformin has been proposed as a treatment for HD patients because genes related to diabetes, such as GLUT1, GLUT3, and insulin, have been found to be altered in HD, and metformin is approved for the treatment of diabetes. Metformin has been shown to exert positive effects on insulin levels and metabolic health by activating AMPK, an enzyme that regulates energy balance. AMPK helps neurons survive by initiating cell repair. AMPK also induces autophagy and reduces aggregation, all of which are crucial for mitigating HD symptoms. The primary outcome of this trial is to observe the impact of metformin on specific tests related to cognitive abilities utilizing the Unified Huntington's Disease Rating Scale.[33] The efficacy of metformin was measured using The Symbol Digit Modalities Test. The Symbol Digit Modalities Test has become a popular test used to examine neuropsychological behaviors. During the test, the speed at which a person processes information is examined using symbol or digit substitution.[34] The verbal fluency test assesses how many words starting with a particular letter a person could say in under a minute. [35] Lastly, the Stroop test was used to observe the responses of an individual to specific stimuli such as colors.[33]

Dextromethorphan/Quinidine

"Evaluating the Efficacy of DM/Q in Treating Irritability in Huntington's Disease" (clinical trial ID NCT03854019) is a phase 3 trial designed to test the effect of DM/Q on pseudobulbar affect (PBA), also known as emotional lability. *Trial* NCT03854019 started August 2019 and ended November 2022. [36] The study enrolled 20 individuals and was designed to assess the efficacy and safety of a dosage of 20 mg/10 mg. The primary outcome was measured using the Irritability Scale, ranging from 0 (not irritable) to 42 (highly irritable).[16]

Deutetrabenazine

"Impact of Deutetrabenazine on Functional Speech and Gait Dynamics in Huntington Disease" (clinical trial NCT04713982) is a phase 2/3 clinical trial testing the effects of deutetrabenazine on patients with HD. [37] Deutetrabenazine is a drug that promotes the storage

of monoamines (dopamine, serotonin, histamine, and norepinephrine) within presynaptic vesicles. Deutetrabenazine has a favorable tolerability profile. The clinical trial started November 2021, and has been estimated to conclude by the end of August 2024. In this phase 3 trial, deutetrabenazine was tested to evaluate its efficacy and safety for controlling HD-associated chorea. A score higher than 8 on the Unified Huntington's Disease Rating Scale (UDHRS) indicates that a patient has higher levels of chorea. Preliminary results of the trial suggest that deutetrabenazine is associated with improvements in chorea. Within 12 weeks of the phase 3 trial, HD patients given deutetrabenazine showed an improvement in the mean maximal chorea score from 12.1 to 7.7. A lower number indicates that the medication is effective in reducing chorea symptoms within an individual. [16]

Pridopidine

"A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients With Early Stage of Huntington Disease" (clinical trial NCT04556656) tested the use of pridopidine on patients with HD. Trial NCT04556656 started October 2020 and ended March 2023.[38] Pridopidine is a dopamine D2 receptor ligand. Pridopidine has been shown to improve motor performance and offer neuroprotective effects like removing toxic proteins and protecting neurons from damage.[16] The trial started October 2020, and ended March 2024. [38] Scientists undertook a 6 month, randomized placebo-controlled trial to assess the efficacy of pridopidine in the treatment of motor deficits in patients with HD. The safety and tolerability profile of pridopidine were assessed. Patients were randomly assigned either the actual medication or the placebo. The study did not provide evidence of efficacy. However, it did show a potential effect of pridopidine on the motor phenotype of HD. Also, pridopidine up to 90 mg per day was well tolerated in patients with HD. [39]

NestaCell

"Phase III Efficacy and Safety of NestaCell® in Moderated Huntington's Disease" (clinical trial NCT06097780) was created by the Butantan Institute and Cellavita. The primary outcome measure of this clinical trial is on the efficacy of NestaCell as measured by the Primary Efficacy Objective. Trial NCT06097780 was initiated in June 2024 and is estimated to end September 2025. NestaCell therapy involves the transplantation of Human Dental Pulp Stem Cells (hDPSCs) into areas in the brain with damaged neurons. NestaCell was given to patients with HD. Depending on their weight, patients were given a specific number of cells. Patients weighing 50 to 67.9 kg will receive 100 million cells (or placebo) and those weighing above 68 kg will receive 136 million cells(or placebo) per administration. Preliminary results suggest

NestaCell improvement in motor scores and functional capacity as measured by the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS TMS). [40]

Analysis of Treatments

Overall, each treatment discussed above is designed to target a specific aspect of the proposed pathophysiology of HD. After researching each treatment option, AAVs, CRISPR, stem cell therapy (Cellavita and NestaCell), and pridopidine appear to hold the most promise for the treatment of HD due to their focus on targeting prominent aspects of HD pathogenesis. Along with these medications, it is also crucial to develop therapies targeting DNA damage and elevatedROS levels, as ROS levels lead to mitochondrial dysfunction, vesicle trafficking, protein misfolding, and cell death. Furthermore, it seems that improving mitochondrial function could also mitigate the symptoms of HD as the mitochondria are severely impacted by HD. These treatments would have to consist of a therapy that targets one specific aspect of HD pathophysiology without harming other physiological processes of the human body. This is where AAVs could potentially come into play and help bring these treatments to their desired area, as AAVs are also a promising potential therapeutic treatment for HD.

5. Conclusion

HD is a rare, incurable, and malignant genetic disorder. Extensive research is required to identify novel treatments and potential cures for HD. HD pathogenesis is complex and involves somatic mutations regarding the CAG trinucleotide expansions in the HTT due to the inability of dna repair, protein misfolding and formation of aggregates, mitochondrial dysfunction due to increased ROS, issues regarding autophagy. It is vital that scientists continue to perform research on HD and HD treatments in order to understand the disease better and come up with a solid treatment for this particular disease. The principal challenges for the future of research in the field of HD consists of finding a treatment that will cure HD.

While there are numerous clinical trials in place to identify a potential treatment, these clinical trials have limitations. The biggest limitation is that these drugs only target a specific symptom of HD. In order for these medications to be efficacious and worthwhile towards an HD patient’s life, it is pivotal to generate drugs and therapies that will directly target the mHTT. If we don’t specifically target the mHTT, these treatments will not be able to truly mitigate HD symptoms and help cure it in individuals with HD. This is especially important because if we can find treatments for HD, then these treatments can potentially be applied to other neurodegenerative diseases, as most neurodegenerative diseases, such as Alzheimer’s, are yet to have a functioning cure. Therefore, with the urgent need to develop a cure for HD, the use of CRISPR and AAVs appear to be the most promising treatment methods due to their ability to

directly target the mHTT. Overall, it is vital that scientists continue to spend time researching HD to a further extent in order to uncover more about the disease, find a cure to increase the survival rate of patients with HD, and potentially apply these findings to the field of neurodegenerative diseases so that individuals with these neurodegenerative conditions can be provided with the opportunity to continue living their lives.

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