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HUNTINGTON'S DISEASE: GENETIC BASIS, CLINICAL MANIFESTATIONS, AND EMERGING THERAPEUTIC APPROACHES

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ABSTRACT

Huntington's disease (HD) is a hereditary, autosomal-dominant neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4. The mutation leads to the production of mutant huntingtin protein (mHTT) with an abnormally long polyglutamine sequence, resulting in neuronal toxicity, particularly in the striatum and cerebral cortex. Clinically, HD manifests with progressive motor disturbances such as chorea and dystonia, along with cognitive decline and psychiatric symptoms, including depression and anxiety. The disease can appear as adult-onset, typically between 35 and 50 years, or as a more aggressive juvenile-onset form. Diagnosis involves genetic testing for CAG expansion, supported by neuroimaging to identify striatal atrophy. Although there is no cure, management focuses on symptom control using dopamine modulators like tetrabenazine, antidepressants, and supportive therapy. Current research emphasizes disease-modifying strategies such as RNA/DNA-targeting therapies, antisense oligonucleotides (e.g., tominersen), gene therapy (AMT-130), and neuroprotective agents, including minocycline and cannabinoids. Investigational treatments targeting mutant huntingtin reduction and enhancing autophagy offer potential future benefits. Despite advances in understanding its complex pathogenesis involving transcriptional dysregulation, protein aggregation, and neuroinflammation, HD remains a fatal disorder with a typical survival of 15–20 years post-onset. Continued exploration of molecular mechanisms and targeted therapies provides hope for delaying progression and improving the quality of life for affected individuals.

KEYWORDS: Huntington's disease, mutant huntingtin, neurodegeneration, gene therapy.

INTRODUCTION

Huntington's disease is the commonest monogenic neurodegenerative disorder of the central nervous system, with a genetic autosomal-dominant inheritance, which first involves the basal ganglia (caudate nucleus and putamen) (1,2). It was first described in detail by George Huntington in 1872.[1] It results in an expanded CAG trinucleotide, causing its repeat in the HTT (huntingtin) gene, identifying the pathogenetic agent — a mutant form of the multifunctional protein huntingtin. The CAG genetic expansion corresponds with the mutant huntingtin's excessively long polyglutamine (polyQ) sequence; the protein has toxic features that lead to neuronal damage and death.[1,2] HD is due to mutations in the HTT gene encoding huntingtin, a ubiquitously expressed protein of 350 kDa. However, the CAG repeat number only partially explains 65%–71% of the variance in the age of onset, which also appears to be influenced by additional environmental and genetic factors, such as modifier genes. Moreover, monozygotic twins have been reported to show different clinical symptoms, suggesting that epigenetic factors or tissue-specific variation in CAG repeats, because of somatic instability, may influence the disease. Huntingtin is a 350 kDa protein containing the polyglutamine sequence at the NH2 terminus and multiple consensus sequences called HEAT (huntingtin, elongation factor 3, protein phosphatase 2A, and TOR1 [target of rapamycin 1]) repeats that are important for protein–protein interactions.[3] HEAT motifs have a helix–turn–helix structure that is tightly packed to form a superhelix hydrophobic core that resists dissociation after proteolytic cleavage. Huntingtin is a cytoplasmic protein with partial nuclear localization. Recently, its nuclear localization sequence (NLS) has been described in the NH2 terminus of the protein.[4] The disease is characterized by motor, cognitive, and psychiatric disorders. Typically, the motor defects include chorea and loss of coordination. Psychiatric symptoms, such as depression, psychosis, and obsessive–compulsive disorder, are also common in HD, particularly distressing for patients, and a range of somatic symptoms. Cognitive decline and bed rest are the results of progressive deterioration. About 20 years after the beginning of symptoms, death occurs.[2,3] HD is characterized by a general shrinkage of the brain and degeneration of the striatum (caudate nucleus and putamen), with specific loss of efferent medium spiny neurons (MSNs). Despite the striatum appearing to be the most afflicted area of the brain, HD patients showed a regionally localized thinning of the cortical ribbon.

Huntington's disease (HD) can be categorized into adult-onset and juvenile-onset forms based on the age of symptom onset and disease progression. Adult-onset HD is more prevalent, presenting motor symptoms like chorea and dystonia, and cognitive and emotional manifestations. It generally advances slowly, with an average life expectancy of 15-20 years. Juvenile-onset HD, less common but more aggressive, typically presents symptoms in childhood or adolescence, with rapid progression and severe motor and cognitive symptoms. This type of HD can lead to significant disability and a shorter life expectancy.[5]

As the illness progresses, this loss of cortical mass moves from the posterior to the anterior cortical areas, marking an early occurrence in HD pathophysiology. This regionally localized cortical degeneration may account for the range of clinical symptoms in HD. Additional features are often present in HD patients, such as weight loss, skeletal-muscle wasting, and cardiac failure.[3] HD is currently classified into three categories: manifest, prodromal, and presymptomatic. People with the CAG expansion but no HD-related symptoms or indicators at the moment are considered presymptomatic HD. People with CAG expansion who have nonspecific or potential motor impairments on examination and slight but noticeable cognitive alterations are considered to have prodromal HD. HD is a clinical diagnosis made through the evaluation of family history, personal history, neurological and psychiatric examination, and genetic testing.[6,7] There is currently no approved disease-modifying treatment for HD.[2] Although symptomatic

treatment can improve quality of life, there is no disease-modifying intervention to prevent the onset or delay the progression of HD.[8] Each patient's symptoms can be unique, hence there is no standardized treatment with medication prescribed on a case-by-case basis, and an extensive range of medications is used to treat each of the unique symptoms. Side effects from medications used to treat HD can also affect each patient differently.[9]

EPIDEMIOLOGY

HD is relatively rare, with an estimated prevalence of 5–10 cases per 100,000 individuals in most European countries, South America, North America, and Australia. HD has a prevalence of 10.6-13.7 individuals per 100,000 in Western populations. The incidence of HD is significantly lower in Japan, Taiwan, and Hong Kong, with prevalences of 1–7 cases per million. In South Africa, black communities had lower rates than white and mixed populations.[10] Based on research conducted between 1985 and 2010, the estimated pooled incidence of HD is 0.38 per 100,000 person-years (95% CI: 0.16–0.94), whereas the global general prevalence is 2.71 per 100,000 (95% CI: 1.55–4.72). 4 More recent research indicates that prevalence is rising in several areas. In 1988, a survey of 2835 HD patients discovered that 40% of patients had depression at the time of the study, while 50% had sought clinical help for depression in the past.[10] With an average start age of 35 to 50 years, HD usually appears in mid-adulthood, while cases with juvenile onset can happen considerably earlier. Patients' personal and familial lives are greatly impacted by the condition. After symptoms appear, patients typically have a 15–20 year life expectancy.

In the past, HD was diagnosed clinically when there was a positive family history of the illness. After the identification of the underlying genetic mutation in 1993, diagnostic testing became widely available. As a consequence, the ascertainment of HD in populations has increased, and the measured prevalence of HD in several populations is substantially higher in the post-diagnostic testing era. Studies performed before 1993 may therefore underestimate the true prevalence of HD.[11]

ETIOLOGY

An autosomal dominantly inherited expansion of the CAG trinucleotide repeat in the huntingtin (HTT) gene on chromosome 4 is the cause of HD. The result is a mutant huntingtin (mHTT) protein with an abnormally lengthy polyglutamine repeat. While reduced penetrance is observed between 36 and 39 repeats, those with more than 39 CAG repeats are guaranteed to develop the disease. When the gene is inherited from the father, a child can have an extended pathogenic repeat length if the father has an intermediate CAG repeat length. Male sperm exhibit larger repeat sizes and higher repeat variability than somatic tissues.[10]

CLINICAL PRESENTATION

A wide range of symptoms have been documented, most of which lead to a decline in motor function, cognitive capacity, behavior, or a combination of these. The majority of HD symptoms fall into one of three categories: behavioral, cognitive, or motor. In the early and mid-phases of the illness's course, motor symptoms include chorea; however, as the disease progresses, movements become less frequent (hypokinetic) and slower (bradykinetic).[12] Alternatively, behavioural symptoms include depression, apathy, and anxiety. Psychosis, aggressiveness, and obsessive-compulsive behavior are some of the less prevalent mental health symptoms. As cognitive symptoms, memory impairments and a reversal of thinking, processing, and organization may manifest. Additional signs may appear, such as inadvertent weight loss and trouble sleeping.

The motor symptoms and signs: Motor alterations are characterized by undesired, involuntary motions. Walking becomes wobbly, and the individual may seem a little drunk in daily life. Initially, the movements often occur in the tiny face muscles as well as the distal extremities, such as the fingers and toes. These muscle twitches are frequently undetectable to onlookers or may be attributed to nervousness. The undesirable motions gradually extend to every other muscle, moving from the distal to the more proximal and axial regions. For certain people, choking can occur at any time as speaking and swallowing become increasingly difficult. As the illness progresses, dysarthria and dysphagia become increasingly noticeable. Every patient has stiffness, hypokinesia, and akinesia, which cause them to move more slowly throughout all activities (bradykinesia: slowness of movement) and to be extremely hesitant to initiate a movement (akinesia: trouble initiating movements). Slower motions with elevated muscle tone, such as torticollis, as well as trunk or limb rotation, are hallmarks of dystonia. Additionally, everyday tasks, including sleeping, showering, dressing, using the restroom, cleaning the house, cooking, and eating, grow harder and harder.[13]

Behaviour and psychiatric symptoms and signs: In the early stages of the disease, typically before motor symptoms appear, psychiatric problems are highly common. These symptoms and indicators often have a very detrimental effect on functioning and the family in day-to-day living.[14] The most prevalent symptom of HD is depression, which can cause lethargy, apathy, and weight loss. Common symptoms include worry, guilt, and low self-esteem. Premanifest gene carriers and those with early symptoms are more likely to commit suicide. A common cause of anxiety is uncertainty regarding the onset or progression of the illness. Aggression and irritability are typical symptoms. Later phases may see the onset of psychosis, which is frequently accompanied by cognitive deterioration. The clinical presentation resembles that of schizophrenia, including auditory and paranoid hallucinations.

Dementia: Cognitive decline is a main sign of dementia, affecting executive functions and causing difficulty in organizing life and making mental adjustments. Patients with HD lose the ability to distinguish between relevant and irrelevant information, leading to complicated situations and impaired language and memory. This cognitive decline can be mild in advanced stages of the disease.[15]

Juvenile Huntington's disease (JHD): A hereditary condition known as juvenile Huntington's disease (JHD) is typified by abnormalities in motor activity, learning, and behavior. It may be classified into three stages: at-risk, preclinical, and clinical. It is frequently observed in juveniles under the age of twenty. The premanifest gene-positive stage, transition, and phenotypic conversion phase are the three stages of the disease's progression. Many years before motor symptoms appear, the earliest indications may be mental and cognitive abnormalities. Additionally, patients may develop depression or burnout, which are progressive changes in behavior and performance at work. Given our growing understanding of genetic status and the progression of the illness, these symptoms may be the initial indication of JHD.[16]

HD PATHOGENESIS

HD is primarily hypothesized to result from a harmful gain-of-function of the mHTT protein.[17] The extension of the CAG repeat causes the N-terminal segment of the protein3 to have an expanded polyglutamine (polyQ) tract, which leads to abnormal folding and accumulation of mHTT in brain cells.[1] It leads to progressive disruption of neuronal physiology. After that, before motor symptoms appear, there is noticeable atrophy in the subcortical white matter and the basal ganglia nuclei, which include the caudate, putamen, globus pallidus, and subthalamic nuclei. There is also noticeable neuronal loss in the cortical, thalamic, and hypothalamic regions, as well as eventually across the entire

brain as the illness worsens.[18] The N-terminal fragment or exon 1 of mHTT containing polyQ repeats can be generated through proteolytic cleavage, and it is widely accepted that this cleavage process plays a significant role in the formation of mHTT N-terminal fragments and subsequent aggregates.[19] There is also oxidative stress with peripheral and central inflammation from the earliest stages of the disease. In addition, mHTT reduces signalling mediated by brain-derived neurotrophic factor (BDNF) by altering transcriptional regulation and axonal transport. furthermore, HD is associated with indications of synaptic dysfunction and changes in cortical glutamatergic and striatal dopaminergic neurotransmission.[1,20,21]

On the other hand, an excessive number of CAG repeats can affect the splicing of mutant *HTT* (*mHTT*), resulting in the generation of a truncated transcript known as HTT exon 1 through abnormal splicing. In addition to being found in human tissues and HD mouse models, aberrantly spliced HTT exon 1 was also found in the striatum, cortex, hippocampus, and cerebellum in a recent study employing an HD knock-in (KI) pig model. Thus, the contribution of mHTT N-terminal fragments or mHTT exon1 products produced by aberrant splicing to the pathogenesis of HD requires further investigation.[22]

Abnormal Protein–Protein Interactions

HTT has direct or indirect interactions with several intracellular proteins that are involved in chromatin architecture, membrane trafficking, signal transduction, and protein translation. HAP1, HAP40, HIP-1, syntaxin-1B, vesicle-associated membrane protein 2, SNAP25, NSF, and synapsins 1 and 2 are only a few of the protein–protein interactions that rely on the polyQ sequences found in HTT. The stability and levels of these protein interactions are altered by mHTT, potentially leading to the dysregulation of intracellular signaling pathways, gene expression, synaptic function, and cellular functions. Furthermore, changes in brain cholesterol homeostasis have been linked to the aberrant protein–protein interactions brought on by Mhtt.[23]

Transcriptional Dysregulation

Transcriptional dysregulation in HD is caused by toxic mHTT, which disrupts protein-protein interactions and alters chromatin structure or genomic DNA, leading to gene expression abnormalities. The polyQ repeats form insoluble aggregates that interact with transcription factors, such as CREB and Sp1, and can enhance HTT-DNA interactions, causing abnormal expression of specific mRNA species.[24]

Autophagy Dysfunction

Aggregated mHTT disrupts autophagy, leading to waste accumulation and impaired protein degradation. J3, an autophagy inducer, has shown potential as an antibody therapy for HD. In vivo studies show J3 treatment reduces mHTT levels in the striatum and increases DARPP-32 levels. Autophagy activators like rapamycin, lithium chloride, and trehalose also show promise in treating HD.[25]

DNA Damage Repair

The progression of HD is believed to be influenced by the expansion of CAG/CTG repeats in somatic tissues. DNA repair genes, such as FAN1, LIG1, MLH1, MSH3, PMS1, and PMS2, play a crucial role in HD progression. FAN1 is associated with delayed onset and slower progression, while MSH3 is key for repeat instability.[26]

DIAGNOSIS OF HD

Diagnosing HD has historically relied on clinical assessments, including the observation of motor symptoms, psychiatric disturbances, and cognitive decline.[27] These symptoms, however, become more noticeable as the illness worsens, making an early diagnosis difficult. The CAG repeat expansion in the HTT gene may now be directly identified, offering a conclusive diagnosis, thanks to advancements in genetic testing.

Differential Diagnosis: Differential diagnosis of Huntington's disease (HD) is crucial as symptoms can be caused by various conditions. Some conditions that may be considered include Parkinson's disease, dementia, schizophrenia, Wilson's disease, and multiple sclerosis. Parkinson's disease is characterized by tremors, rigidity, and difficulty with movement, while HD symptoms are often asymmetrical and do not respond well to medication. Recent advancements in gene prioritization strategies have shown the importance of consensus strategies in unraveling the pathogenesis of neurodegenerative disorders. These strategies help identify biologically significant genes, offering potential targets for understanding the pathogenesis of degenerative diseases and developing targeted therapeutics. The success of these strategies in identifying genes directly associated with the disease and those involved in relevant biological processes echoes the potential applicability of similar methodologies in HD research, augmenting efforts to understand the intricate mechanisms underlying the disease's progression and potentially uncovering novel targets for intervention and therapy.[28,29]

Brain imaging: Brain imaging is crucial for diagnosing and understanding HD, with MRI being a primary modality used. It provides insights into structural and functional alterations in the brain, allowing clinicians to detect abnormalities. Common findings include atrophy of the striatum, particularly in the caudate nucleus and putamen, which contribute to HD diagnosis.

EEG signal: EEG can help differentiate HD from other neurodegenerative disorders like Parkinson's disease by revealing differences in electrical brain activity patterns. While not specific to HD, the combination of clinical symptoms and EEG abnormalities can aid in diagnosis and rule out other conditions. EEG also tracks HD progression and evaluates potential treatments.[30]

MANAGEMENT

The field of potential future HD therapies is advancing rapidly and holds an exciting future. Currently, attention is particularly focused on lowering mHTT through RNA and DNA targeting therapies. Of these, antisense oligonucleotides are the most rapidly advancing potential therapies.[31,32] Research on immunomodulatory and anti-inflammatory therapies in Huntington's Disease (HD) has mainly involved preclinical studies using in vitro cell cultures and animal models to explore their potential effects. For instance, chronic treatment with the selective cyclooxygenase (COX) 2 inhibitors celecoxib and meloxicam attenuated behavioral and biochemical changes in a quinolinic acid-induced rat model of HD.[33] Minocycline and cannabinoids have also been tested in HD. Minocycline is a second-generation tetracycline that has been in therapeutic use for over 30 years. In addition to its antibiotic properties, minocycline can exert a variety of biological actions, including anti-inflammatory and antiapoptotic activities. A meta-analysis indicates that minocycline provides neuroprotective effects in rodent models of neurodegenerative diseases, including Huntington's disease (HD), due to its anti-inflammatory, antiapoptotic, and antioxidant properties.[34] Minocycline 200 mg/day was considered safe and well-tolerated in a 6-month treatment protocol. Here again, no noticeable changes were reported in cognitive and motor symptoms as evaluated by the Mini-Mental State

Examination, UHDRS, and Abnormal Involuntary Movement Scale.[35] Due to their anti-inflammatory properties, cannabinoids have been studied as a potential therapeutic approach in neuroinflammatory diseases.[36] The use of cannabidiol was considered safe and well-tolerated in a clinical trial conducted for 6 weeks with 15 patients with HD. Again, no significant improvement in clinical outcomes was observed.[37] The expert opinions on HD motor symptom treatment have allowed for the generation of an algorithm for HD motor management. Previous treatments of HD-related motor symptoms are directed at reducing and avoiding increased stiffness.

Treatment of behavioral disorders: Cognitive dysfunction in HD is characterized by slowness in thinking, called subcortical dementia. Patients also experience problems planning or making mental changes in their lives, as well as a loss of mental flexibility and the capacity to discern whether matters are more or less significant. It appears that memory is untouched for longer. The most common psychiatric feature of HD is depression, which competes and is often confused with apathy. Even among gene carriers, the prevalence of depressed mood in HD is much higher than in the general population; in affected individuals, it has been reported to reach 69%, and its highest frequency was noted when patients began to lose their independence as a result of decreased functional capacity. Treatment of depression in HD does not differ from standard treatment of depression and is based on the usage of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) with venlafaxine, which has confirmed efficacy.[38] SSRIs are the first-choice class of drugs for the treatment of depression in HD and have been reported to be effective in the treatment of irritability and obsessive-compulsive behaviors.

Currently, HD does not have a cure, and the available treatments primarily aim to manage psychiatric and movement symptoms. We review the current state of potential therapies for HD, encompassing pharmacological interventions, strategies to reduce mHTT, stem cell transplantation, and gene therapy.

Dopamine Modulation: In the treatment of HD, dopamine modulation is essential, especially when it comes to HD-associated chorea. The fundamental idea behind dopamine modulation in HD therapy is the dysregulation of dopamine signaling in the basal ganglia, a part of the brain involved in motor control.[39] Dopamine transporter inhibitors have been approved for treating HD by targeting the DAT, which reuptakes dopamine from the synaptic cleft. These medications reduce dopamine reuptake, increasing dopamine availability, normalizing dopamine signaling, and alleviating motor symptoms like chorea. Tetrabenazine and deutetrabenazine have shown efficacy in reducing chorea severity and improving motor function.[40]

Glutamate Receptor Modulation: Glutamate receptor modulation is a promising therapeutic approach for treating HD, which is linked to abnormalities in glutamate signaling, particularly excessive activation of NMDA receptors. NMDA receptor antagonists, like memantine and amantadine, block excessive activation of NMDA receptors, improving motor function and reducing neurodegeneration in HD. However, their use in chorea treatment remains controversial. Another approach involves modulating metabotropic glutamate receptors (mGluRs), with mGluR5 activation implicated in HD pathology. Antagonists of mGluR5, like AFQ056, are being investigated as potential therapeutic agents.[41]

Other Therapies: Curcumin, a phytochemical commonly found in Asian food, has been shown to possess a wide range of beneficial properties, including antioxidant, anti-inflammatory, and anti-fibrogenic effects. Research has demonstrated that curcumin effectively alleviates disease symptoms in a Drosophila model of HD by suppressing cell death. Inflammation is commonly observed in HD patients before the onset of symptoms. Certain drugs, such as

neflamapimod and minocycline, have been investigated for their potential to improve glial cell functions and prevent neuroinflammation in HD patients.[42]

Cell replacement therapy: The safety and efficacy of cell replacement therapy in humans have been studied and confirmed, but only in small cohorts. There is therefore an urgent need for a well-designed multicenter study to validate the efficacy of this approach. Although many cell sources for the treatment were investigated, the clinical standard at this time appears to be primary fetal cells isolated from ganglionic eminences (GE) around 7–10 weeks post-conception. The window of time is crucial because grafts must form strong synaptic connections with their appropriate destinations in the host brain and be correctly targeted by host axons. Typically, the grafts are small and cover less than 4% of the volume of the corpus striatum; however, their size has not been standardized and may differ from patient to patient. Different types of adverse effects were reported with respect to brain cell transplants, which could also have been caused by the surgical procedure (subdural hematoma, intracerebral hemorrhage), allogeneic immune reactions, infections (e.g., contamination with vaginal flora), or abnormalities in the grafted tissue (cyst formation, graft overgrowth).[43]

Clinical trials for HD treatment are currently underway, with specific objectives aimed at evaluating the safety, effectiveness, and potential benefits of various therapeutic approaches.

Tominersen: Tominersen, an ASO developed by Ionis Pharmaceuticals, targets HTT mRNA to reduce mHTT production. The GENERATION HD1 clinical trial showed promising results in reducing mHTT levels in the CNS and slowing disease progression. However, Roche discontinued dosing in the Phase III study in March 2021. The GENERATION HD2 trial, focusing on younger participants with lower disease burden, aims to assess the potential benefits of this dosing regimen. The trial is expected to be completed in 2027.

AMT-130: UniQure is developing AMT-130, a gene therapy targeting HTT expression in the brain. Preclinical studies show promising results in reducing mHTT levels and improving motor function. However, a Phase 1/2 trial reported severe adverse effects in three out of 14 patients, leading to suspension of dosing. A Phase 3 clinical trial is ongoing to assess safety and efficacy. Further investigation will focus on using two doses in combination with perioperative immunosuppression.[44]

VMAT Inhibitor: SOM3355 and Valbenazine: Bevantolol hydrochloride, another name for SOM3355, is a VMAT inhibitor that interferes with dopamine transmission between neurons. A mixed-model analysis showed a notable improvement in the total maximum chorea score in a prior small study, suggesting that it may be used to successfully manage HD chorea. After a clinical phase 2a trial concluded, SOM3355 showed no depressed side effects and a good safety profile. To confirm the medication's effectiveness and safety in HD patients with chorea, a phase 2b study is now underway.[45]

Pridopidine: Pridopidine, a dopamine stabilizer, has shown positive effects in preclinical studies, including increased expression of pro-survival and neurostimulatory molecules in R6/2 mice and reduced size of mHTT aggregates in striatal tissues. A study called PRIDE-HD showed a beneficial effect on Total Functional Capacity, particularly in early-stage HD participants. However, PROOF-HD showed mixed results, with clinically meaningful benefits and

improvements in disease progression and motor and cognitive outcomes compared to placebo. Further research is needed to fully understand pridopidine's effects in different patient populations and treatment contexts.[46]

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