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Review Article

HUNTINGTON'S DISEASE: CURRENT ADVANCES AND FUTURE PROSPECTS

BRIGHT LEMUEL JOHN N[1*], AKILA RAMANATHAN[2]

[1]College of Pharmacy, Madras Medical College, Chennai, Tamil Nadu, India, [2]Department of Pharmaceutical Biotechnology, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu, India
Email: brightlemu@gmail.com

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ABSTRACT

Huntington's disease is a neurodegenerative disease which is caused by dominantly inherited cytosine-adenine-guanine trinucleotide repeat expansion in the huntingtin gene of chromosome 4. Present survey reveals 2.7 per 100000 people are affected by huntington's disease worldwide. The symptoms present with these patients are progressive motor, cognitive and psychiatric disorders. The early symptoms are chorea and loss of balance. This review aims to observe the present data available concerning huntington's disease, symptoms, age of onset, risk factors, benefits of early diagnosis and genetic attribution. There is no cure for the disease. The article searched, selected and reviewed were from google scholar, medscape, NIH MedlinePlus, PubMed database using MeSH terms huntington's disease, recent therapeutic advancement from 2003 to July 2021 with no language restriction and additional studies were included from the reference lists of relevant articles. The present review provides clinical features, diagnosis, symptomatic management and ongoing research. Hence this review will have an impact to create awareness for the society and researchers to find future treatment for Huntington's disease.

Keywords: Huntington's disease, Symptom, Gene, Treatment

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INTRODUCTION

Huntington disease (HD) is a highly defective neurodegenerative disease which includes symptoms like progressive motor, cognitive and psychiatric disorders. It occurs by the repetition of cytosine, adenine and guanine (CAG) trinucleotide on the chromosome 4p16.3 in the huntingtin gene [1]. This huntingtin gene gets translated into a mutant huntingtin protein (mHTT) [2]. In HD the symptoms are analogous to several other diseases. The family history plays a major role in HD patients, though there are 1-3% patients that have no family history [3]. There is a 50% chance of inheriting the huntingtin gene from parents to children. Inheriting the gene develops the disease [4,5]. HD can be classified into Adult onset huntington's disease and Juvenile Huntington's disease (JHD). Adults in the long run develop the symptoms in their mid 30s and 50s whereas symptoms of JHD are alike to Parkinson's disease which constitute about 5% of HD cases [6]. The learning difficulties at school are the first sign and the majorities have epileptic fits. In HD 75% of father plays a major role in transmitting the disease to their children [7]. Nearly 2.7 per 100000 people are affected by HD worldwide. The patients with more CAG repeats exhibit this disease. This review is to find the aetiology, pathophysiology, types of diagnostic tests, clinical classification, management and ongoing research for management of HD [8, 9].

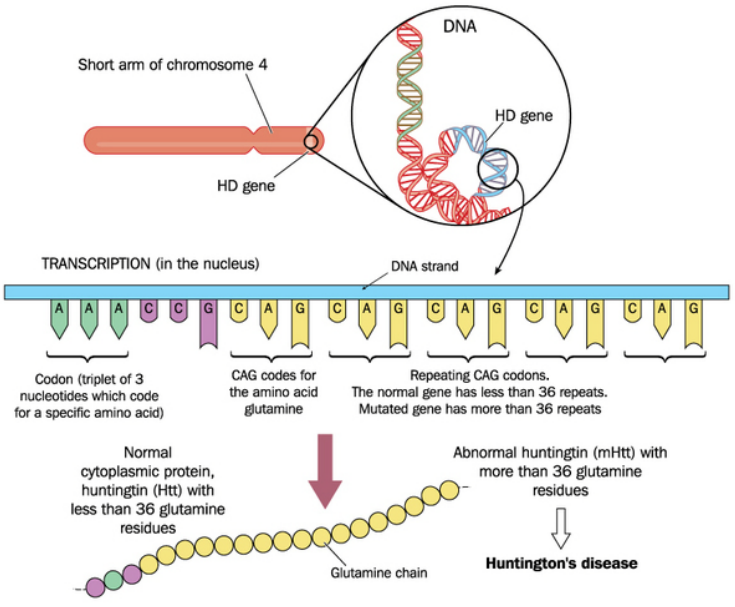

Fig. 1: Schematic demonstration of gene mutation causing Huntington's disease [10]. 1. Cytosine, adenine, and guanine (CAG) trinucleotide repeats on the short arm of chromosome 4p16.3 in the Huntingtin (HTT) gene having less than 36 repeats. 2. Expansion of unstable trinucleotide repeats 36 and above on HTT gene causes huntington's disease

Aetiology and pathophysiology

HD is mainly caused by elongation of CAG repeats of chromosome 4p16.3 in the huntingtin gene. Patients affected with HD can be identified by genetic testing because HD is linked with the number of CAG repeats [11]. Patients with 36 repeats or more are affected by this disease. Whereas in JHD the CAG repeats are more than 55 predominantly. The length of CAG from 29 to 35 does not cause the disease but it can lengthen in the generations. The male parent is the major cause for inheriting the disease [9].

The majority of signal in HD occurs within the neostriatum. The degrees of atrophy depends upon pathological grade in various regions such as basal ganglia, frontal cerebral cortex, globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cerebellum [12]. In mouse model the pathophysiology was studied and it was observed that in early HD there is an increase in inhibitory input with a little change in excitatory input to pyramidal neurons but in late HD there is a marked decrease in inhibitory inputs to pyramidal neurons and a concomitant increase in excitation. In early HD the dopamine inputs to direct medium spiny neurons increase both excitatory and inhibitory inputs via a presynaptic effect. But there is a decrease in indirect receptor function on indirect pathway medium spiny neurons, but no net presynaptic change. An increase in evoked excitatory post-synaptic currents occurs that is probably mediated post synaptically. In late HD there is a decrease in excitation to both direct and indirect medium sized-spiny neurons which is probably due to a disconnection from excitatory synaptic inputs. There also is an increase in inhibitory input, but only to indirect medium sized-spiny neurons [9].

Age of onset

There are 2 types of onsets. The early onset occurs between the age of 20 to 30 y whereas the late onset is between 30 to 50 y. The length of the CAG repeat in the late onset is 40 to 49 whereas in early onset the repeat is more than 50. The JHD occurs at the age below 21 and it constitutes about 5% of the cases [13, 14]. The lifetime of the Huntington's disease is 15-20 y, it also varies depending upon the care [1]. The shortening of the telomeres leads to several neurodegenerative diseases. HD leukocytes have the shortest telomeres, among all the neurodegenerative diseases [2]. The following table 1 represents the presence or absence of HD.

Table 1: **Presence or absence of HD depending on CAG repeats**

CAG repeats (length)	Type	Presence/absence	References
>60	Juvenile	Presence of HD	[1,5,7]
Above 39	Adult onset	Presence of HD	[1,5,7]
36-39	Late onset (adult)	Are susceptible to HD	[1,5,7]
10-26	-	Absence	[1,5,7]

Symptoms

Table 2: **Types of symptoms and indications**

Types	Indications	References
Motor symptoms	Chorea, dystonia, loss of postural reflexes, bradykinesia and rigidity	[15-18]
Cognitive symptoms	Disorganization as a result of difficulties with planning, initiating, and organizing thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information	[15-18]
Psychiatric symptoms	Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hypersexuality (uncommon), psychosis (uncommon)	[15-18]
Metabolic symptoms	Weight loss and sleep disturbance	[6]
Miscellaneous	Dysphasia (combination of motor and language difficulties), dysphagia (combination of motor problems, impulsivity, and distractibility)	[15-18]

Diagnosis

The motor symptoms that occur in HD can be diagnosed by the total motor score (TMS) of unified HD rating scale, though TMS does not depict the precise changes when group of people with HD are analyzed. The quantitative motor tests are more accurate [19].

Types of diagnostic tests

Generally, three types of diagnostic testing are used to manifest the HD.

Type I: By collecting patient history and neurological examination. For this a neurologist will conduct a detailed interview to obtain a pedigree to rule out other conditions. And he will do physical examination such as review reflexes, balance, movement, muscle tone, hearing, walking, and mental status. After analysing type I the individual may be referred to specialists such as psychiatrists, genetic counsellors, clinical neuropsychologists, or speech pathologists for specialized management and/or diagnostic clarification [1, 4].

Type II: Diagnostic imaging is normally conducted if a person's family history and genetic testing are inconclusive. In this condition the physician may recommend brain imaging, such as computed tomography or magnetic resonance imaging. As the disease progresses, these scans typically reveal shrinkage in parts of the brain and enlargement of fluid-filled cavities within the brain called ventricles. These changes do not necessarily indicate HD, because they can occur in other disorders [1, 4].

Type III: Genetic tests. Genetic testing can confirm to determine a person's chance of developing or passing on a genetic disorder. Genetic testing makes it possible to predict with a higher degree of certainty if someone will develop HD. The most accurate and effective technique for diagnosis HD is direct genetic test which counts the number of CAG repeats in the HD gene, using DNA taken from a blood sample. The presence of 36 or more repeats supports a diagnosis of HD. A test result of 26 or fewer repeats rules out HD. The prenatal exclusion testing requires a sample of DNA from a parent or relative to identify marker HD gene and to determine if a fetus has inherited a chromosome 4 mutation from an affected grandparent. This method is used for prenatal testing [1, 4].

Patients at risk of HD often test before making decisions about marriage or starting their career. The emotions cannot be determined and can lead to some adverse reactions. In some cases, the patient who is in a serious relationship and is about to marry will have to learn what to tell the mate about his/her genetic disorder. For these young people this seems to end their career and it leads to a disappointment [20].

Quality of life

HD has an intense effect on the quality of life. The onset of symptoms starts with the loss of employment in the early stages of HD. The patient will need a 24 h care and support at the final stages [20]. Physical fitness is necessary and regular exercise can improve the quality of life [21]. Patients with HD at the early stages are not aware

of the choreiform movements, it affects while doing the daily functioning activities. In recent studies the gait impairments, bradykinesia, and choreiform movements are the important health issues that damage the quality of life of patients. The doctors help in consulting the patients and giving them treatment when chorea interferes with the daily activities. The dopamine depleting drugs, or antipsychotics drugs are given to the patient to treat chorea [22].

Management guidelines

To manage symptoms and improve quality of life treatments are needed. Unfortunately, there is no drug available to cure HD. But both drug based and non-drug based treatments are practiced to slow down the disease progression. Drugs commonly used for symptomatic management are olanzapine, risperidone, quetiapine, clozapine, and aripiprazole for psychosis [23]. For depression, anxiety, obsessive-compulsive symptoms, irritability, aggression drugs like citalopram, fluoxetine, paroxetine, mirtazapine and venlafaxine are prescribed. Zopiclone and zolpidem are given for altered sleep-wake cycle [24]. Anticonvulsants like sodium valproate, lamotrigine, and carbamazepine are used as mood stabilizers. Antipsychotic drugs, antidepressant and tranquilizers are used to control HD [18].

Many non-drug based measures are effective in the management of HD, and these are often more helpful than drugs. The physicians, nurses, physiotherapists, speech and language therapists and other health care workers play a major role on these patients. Though the pharmacological effect is not up to the mark both pharmacological and non-pharmacological treatments are necessary. Because of the limited evidence, their use is based on extensive clinical experience. Physiotherapy is normally done to optimize and strengthen gait and balance, and to assess for walking aids. Occupational therapy can be considered to modify home environment and improve safety and weighted wrist bands to combat limb chorea. Occupational therapy is also advisable to overcome apathy and difficulty in initiating activities. Apart from these appoint experienced healthcare professionals to help at home, residential or nursing home care, day centres to maintain social interactions. Speech and language therapy is practiced optimizing speech and to advise on safest food consistencies at different stages of disease. Develop strategies to deal with cognitive and emotional challenges of disease using counselling or cognitive behavioural therapy. Exercise plays a major role in controlling the disease [25]. Physicians are recommended that patients are referred to a specialist multidisciplinary HD clinic wherever it is possible, so that they can access care from healthcare professionals experienced in the management of the disease. Support from professionals in the community remains vital, and optimal care is typically provided by a multidisciplinary team that includes some or all the following: general practitioners, neurologists, geneticists, psychiatrists, physiotherapists, occupational therapists, speech and language therapists, dietitians, community mental health teams, and social workers. Presently HD advisers are available throughout England and Wales to support patients and their families, and to provide educational input for healthcare professionals caring for people with the disease [26]. As the HD progress the dysphagia occurs. Hence it is recommended that a person with HD and their carers seek professional advice to make sure their diet is nutritious, with lots of calories and easy to eat [27].

Table 3: **Therapeutic approaches to Huntington's disease developed by the pharmaceutical companies in current or future multi-site clinical trials**

	Type of approach	Drug/No drug and mode of action	Clinical trial	Hope to society	References
UniQure	Genetic therapies to lower huntingtin	AMT-130: It is delivered by a brain surgery and uses a virus to spread the treatment throughout the brain. The treatment targets the genetic messages of both harmful and normal huntingtin protein, lowering both.	Phase I/II safety trial	Experimental data in small, large animals and three publications which together show good safety, stability, and spread of AMT-130 throughout the brain.	[28, 29]
Novartis	A pill to lower huntingtin	Branaplam: It was developed to treat the neurological disorder spinal muscular atrophy, could be repurposed to treat HD.	Received orphan drug status. Used in a clinical trial to treat people with HD.	Hopefully launched in 2021 itself.	[30]
PTC Therapeutics	A pill to lower huntingtin	PTC518: It reduces the levels of huntingtin in different animal and lab models of HD.	Phase I clinical trial in healthy people is currently underway to investigate the safety of PTC518.	Provisional data shared at a recent investor meeting looks more promising and indicates this therapy is working as expected, and no dangerous side effects have been identified yet.	[31]
Atalanta Therapeutics	New genetic technologies to treat Huntington's disease	RNAi therapies for different neurodegenerative diseases, including Huntington's disease. RNAi therapies work in a similar way to anti-sense oligonucleotides by interfering with a specific genetic message to lower the levels of a specific protein.	-	Atalanta makes a special form of RNAi which has a branched structure and is able to spread well throughout the brain, so they think this will be good for treating brain related diseases.	[32]
Locanabio	New genetic technologies to treat HD	Aims to target genetic messages which contain the instructions for cells to make disease causing proteins, such as the harmful form of huntingtin.	-	More details yet to come and expecting better outcome.	[33]
Annexon Biosciences	Stopping the complement system	ANX005: Therapy targets part of the immune system. People with HD seem to have overactive complement systems that leads to nerve cell damage and changes to the connections between brain cells. This therapy aims to stop the complement system from switching on too much.	Phase II trial underway for Huntington's patients with their drug	Expecting better outcome.	[34,35]

	Type of approach	Drug/No drug and mode of action	Clinical trial	Hope to society	References
Prilenia	Stopping the complement system	Pridopidine: Action on sigma 1 receptor.	Phase III trial	Expecting better outcomes.	[36,37]
Triplet Therapeutics	Stopping CAG repeat expansion	TTX-3360: Targeting DNA damage repair processes, with the aim of slowing or halting the progression of HD. Aims to track HD progression over time and further explore CAG repeat expansion along with the development of symptoms. The main goal is to determine the best time to treat.	-	Expecting better outcome.	[38]
LoQus23 Therapeutics	Stopping CAG repeat expansion	Targeting DNA damage repair processes, with the aim of slowing or halting the progression of HD		Expecting better outcome.	[11,38]
Sage Therapeutics	Targeting the symptoms of Huntington's disease	SAGE-718: developing and validating patient-reported outcome and it involves questions answered directly by patients, rather than measurements made by doctors.	Phase I/II clinical trial	Expecting better outcome.	[39]
Neurocrine Biosciences	Targeting the symptoms of Huntington's disease	Valbenazine: similar to treatments like tetrabenazine and deutetrabenazine and has already been approved for a disorder called tardive dyskinesia.	Phase III clinical trial. KINECT-HD-study valbenazine's effects on the movement symptoms of HD (chorea)	Expecting better outcome.	[28, 40, 41]

Observational and local studies

For understanding HD and identifying new aspects of HD biology to focus on for future drug development observational studies are also in progress. ENROLL-HD is an observational study for HD families that monitors how HD appears and changes in people over time [42]. Through a better understanding of HD, scientists hope they might learn how to make better medicines for HD. Clarity is a cerebrospinal fluid collection initiative to facilitate therapeutic development for HD [43, 44]. Researchers use the exact same methods to collect spinal fluid from participants all over the world, and these samples provide a window into how the nervous system is affected by HD. At present academic groups are also conducting research [PREDICT-HD] on a smaller scale population by collecting family survey and questionnaires, observing communication style and advising genetic testing to improve the quality of life by doing physical therapy and speech pathology regimens, or testing existing drug combinations or alternative therapies to improve side effects or sleep [45, 46].

CONCLUSION

The rare and family disease (HD) has no cure as far now, but treatments can be given through both pharmacological and non-pharmacological methods. Many organisations are there globally, and the clinical trials are on process. To perform the efficacy and safety of the drug right dose is required. More emphasis should be laid on clinical trials of this disease so that more efficient treatments of the disease could be done. Gene therapy can be optimistic. The screening of the embryo for the test tube baby must be enhanced in order to stop the family mutations (disease). It is perpetuity in family, to break this cloud that threatens the family in effort to bring them hope and optimism by doing this together with them as they volunteer to participate in trials it can be useful, though the outcomes are not known. There must be hope in patients, now it's much more than expectations. Expectations lead to disappointment but with hope they can survive. Sharing their sorrow and disappointment can give them hope. The present review would be beneficial for the researchers working in the field of development of new drugs for the treatment of HD and to look forward for more effective strategies to eradicate this difficulty completely. In next 20 y we see that this disease will be cured at the initial stages, within days they are born.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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