



Huntington's Disease- An Updated Review

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ABSTRACT

Huntington's disease (HD) is a rare autosomal dominant, fatal neurodegenerative disorder of the central nervous system characterized by unwanted choreatic movements, behavioural disruption, psychiatric disturbances and dementia. This condition is characterized by progressive degeneration of neurons within the basal ganglia, primarily the caudate and the putamen. As the disease progresses, neuronal losses occur in the white matter, cerebral cortex and thalamus. In this article, the authors reviewed the genetic aspects, etiological factors, stages of the disease condition along with the signs and symptoms, various diagnostic procedures besides with the pharmacological and non-pharmacological management of the Huntington's disease. This disease is inherited within the families, and the pathophysiology of Huntington disease is restricted to the brain, where degeneration begins initially in the striatum, spreads to the cortex and eventually appears throughout the brain. The pathogenesis of this disease is still unrevealed, and there is no treatment available for the cure of the disease. There were many drugs of choices available for symptomatic treatment aiming to improve the quality of life in the patient. The non-pharmacological therapy for managing Huntington's disease includes physiotherapy, speech therapy and psychotherapy. At a therapeutic setting, all the needs of the patients are to be addressed as the advancement in the development of new therapeutic agents are paving the way for the better outcomes in the management of Huntington's disease and thereby promising better healthcare for these patients.



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INTRODUCTION

Huntington's disease (HD) is a rare autosomal dominant, fatal neurodegenerative disorder of the central

nervous system characterized by unwanted choreatic movements, behavioural and psychiatric disturbances and dementia (Raymund, 2010). This condition is characterized by progressive degeneration of neurons within the basal ganglia, primarily the caudate and the putamen (Bilney *et al.*, 2003). As the disease progresses, neuronal losses occur in the white matter, cerebral cortex and thalamus (Vonsattel *et al.*, 1985). Huntington's disease is characterized by both voluntary as well as involuntary movement disorders. Voluntary movements can be affected by bradykinesia and akinesia, resulting in difficulty in initiating movements. Postural stability may also be impaired due to loss of balance during movements resulting in sudden and frequent falls (Kirkwood *et al.*, 2001). Involuntary move-

ments include chorea, athetosis, dystonia and tics and these involuntary movements affect motor function that results in less accurate and clumsy movements (Gordon *et al.*, 2000).

The neuropathological characteristics of Huntington's disease are (i) diffuse atrophy of neostriatum (ii) involvement of caudate nucleus is higher than putamen, (iii) globus pallidus is affected to a lesser extent and (iv) subtle changes occur in the cerebral cortex. The striatum degeneration and disruption of frontal subcortical neural circuits lead to cognitive deficit reflected by difficulty in maintaining (i) attention to a task (ii) planning (iii) initiating activity and (iv) organizing ability which is associated with compromised ability to complete regular tasks. The count of CAG trinucleotide on chromosome number 4 majorly determines the age of onset in Huntington's disease. Disease progression is independent on length of CAG repeats but is closely related to the progress of neuronal loss in striatum. Most of the cases show striatum as the frequently affected area in Huntington's disease but, recent literature manifests a widespread of cortical and subcortical brain atrophy causing functional changes in the brain during the early stages of disease onset. The clinical signs and symptoms of the HD progress with the extent of neuronal dysfunction. Depression and irritability are the vital behavioural characteristics of Huntington's disease. These symptoms have significant effects on the quality of life and social relationships (Thompson *et al.*, 2002).

Genetics

Huntington's disease shows equal impact irrespective of race and gender. Children who acquire juvenile Huntington's disease have rare chances of survival up to adulthood as reports state that the maximum survival chances are about 10-15 years after the onset of disease. Huntington's disease is inherited within the families. If one parent carries the defective gene for Huntington's disease, his/her offspring will have 50% chances of acquiring the lethal gene. Every individual who carries these lethal genes will be susceptible to the development of the disease. In western countries, it is estimated that about five to seven people per 1,00,000 population were affected by Huntington's disease. Japan has a much lower prevalence of Huntington's disease, showing 10^{th} part of the prevalence as in Caucasian population.

Aetiology

Huntington's disease is caused due to a mutation observed in the expression of CAG(trinucleotide) repeats within the coding region of gene "1T15"(interesting transcript). The 1T15 gene,

present on the short arm of chromosome 4, encodes the protein Huntingtin. This gene mutation results in an expanded stretch of CAG repeats, resulting in characteristic motor signs and brain pathology (Bilney *et al.*, 2003; Gusella *et al.*, 1993). A repeat, containing 36 CAG or more results in Huntington's disease with increased prevalence at a decreased age of onset having longer CAG repeats. A large number of individuals exhibiting expanded CAG repeats than healthy individual will actively manifest disease due to adult-onset in the majority of cases. The mutant Huntingtin gene retains some of the basic functions of the normal gene, as the individuals who are homozygous for the Huntingtin gene with only one mutant gene exhibit same clinical functions as heterozygous Huntington's disease patient.

The pathophysiology of Huntington disease is restricted to the brain, where degeneration begins initially in the striatum, spreads to the cortex and eventually appears throughout the brain (Vonsattel *et al.*, 1985). The Huntingtin protein has an anti-apoptotic property which helps in protection from toxic mutants. The mutant form of Huntingtin leads to both loss and gain of function (Trottier *et al.*, 1994). Huntingtin protein has a regulatory role both in inter and intracellular transport. It is preferentially present in brain and testis, while in liver and lungs to a lesser amount. Its distribution varies in different areas of the brain, showing higher presence in the corpus striatum, followed by cerebral and cerebellar cortices (Mahalingam and Levy, 2014).

Gene copying leads to errors and frequently leads to mutations. Though the number of CAG repeats increases with generations resulting in HD among future generations, the number of CAG repeats is directly proportional to the earliest onset of disease. Therefore, infantile HD patients and juvenile-onset patients possess a large number of CAG repeats than their parents (Tabrizi *et al.*, 2009). The relation between the lengths of CAG repeat, age of disease onset depends on the first appearance of clinical manifestations (Wheelock *et al.*, 2003). Intermediate allele shows greater irritability and predisposition of gene expression during spermatogenesis than oogenesis. Therefore, males with intermediate allele have higher chances of producing an offspring with Huntington's disease having greater than 36 CAG repeats. Paternal inheritance is of higher incidence when compared to the maternal impact in juvenile and infantile Huntington's disease (Koutsis *et al.*, 2013).

STAGES OF HUNTINGTON'S DISEASE

People with Huntington's disease follow a disease progression by the onset of symptoms. The patient remains highly functional and initially independent and becomes worse as the disease progresses. The age at which people gets affected varies between person to person. The life course of the person with one of the affected parents with Huntington's disease can be divided into "at-risk", preclinical and clinical stage.

The "at-risk" stage of the person ends when the CAG repeats on chromosome 4 is determined. If the person carries the gene, then he/she transits through preclinical and clinical stages till death. The preclinical stage is categorized into three phases, a transition phase preceded by a pre manifestation stage and "at-risk" stage. During the "at-risk" stage, the person might have anxiety and uncertainty about their future. The "at-risk" stage is followed by the premanifest stage, where the patient might have uncertainty regarding the disease onset, and about their career. In the transition phase, the uncertainty regarding the onset of the disease remains the same, while changes occur in behaviour and motor activity. The patient may develop strong feelings regarding cognitive changes.

The clinical-stage is further classified into three clinical stages. In the first stage, cognitive, psychiatric and neurological symptoms may occur. Chorea is the most prominent symptom in this stage, and rarely death may occur. In the second stage, generalized motor disturbance, physical and psychological dependence becomes a physical burden to the family. Death might occur either due to suicide or euthanasia. In the third stage, generalized motor disturbance and complete physical dependence occurs and finally results in death. The physical or clinical symptoms get severe during stress conditions and fades away as they become relieved. The diagnosis becomes more complicated when the motor signs are less specific (Paulsen *et al.*, 2008).

Signs and Symptoms

Huntington's disease has three subtypes that include adult, juvenile and infantile. Among these three subtypes, adult-onset is more prevalent while the remaining subtypes were quite less common (Ross and Tabrizi, 2011). Adult-onset of Huntington's disease has three pathological domains which characterize the clinical presentations of most of the patients that include cognitive deficits, motor symptoms and psychiatric alterations. The domain which gets affected first and clinical manifestations during the disease may vary.

The clinical presentation of juvenile Huntington's disease differs widely from the typical course of the disease. Especially in young people, it almost becomes impossible for the physicians to differentiate between the age-related alterations and disease-specific motor, cognitive or behavioural disturbances. The clinical manifestations of Huntington's disease might get complemented by less frequent symptoms such as sleep and circadian disturbances, epileptic seizures, dysfunction of the autonomic nervous system and weight loss. Irrespective of the sequence of appearing symptoms and their mechanism, these will get interfered with social activities and their profession (Reetz *et al.*, 2015). The progression of the disease leads to more dependency and finally results in death. Pneumonia is the most frequent cause of death in Huntington's disease since most patients suffer from dysphagia in the advanced stages of the disease; they are more prone to aspiration pneumonia.

Motor Signs and Symptoms

Involuntary and unwanted movements are characteristic of motor changes in Huntington's disease. The involuntary movements occur initially in the distal extremities such as toes, fingers and small facial muscles. These movements gradually progress that spreads from distal to proximal and axial. The motor signs and symptoms include (a) dystonia (b) Chorea (c) bradykinesia/akinesia and (d) eye movements.

Dystonia

Dystonia is the first motor clinical manifestation in Huntington's disease. It is characterized by slow movement with increased muscle tone thus leading to an abnormal posture of a single limb or trunk and reduced voluntary and involuntary activity (Raymund, 2010). The subjects remain stable while at rest & talking due to the absence of dystonia, but in some instances, dystonia might arise while walking. As the disease gets progressed, dystonia becomes predominant by both increased muscle tone and visible abnormal postures of head, trunk & body.

Chorea

Choreatic movements are non-repetitive, arrhythmic and involuntary movements of the facial muscles and the distal extremities predominantly in toes and fingers. These movements begin as small, mild movements and develop into involuntary movements unknowingly. These movements are usually misinterpreted as agitation or nervousness. The movements can be best analyzed when the subject

is at absolute rest or highly concentrated on some tasks since these movements cannot be suppressed voluntarily and associated with motor persistence. There is no single specific pattern existing for choreatic movements. Still, choreatic facial movements lead to continuous movements of facial muscles such as closed eye, bent head, protruded tongue and lifted eyebrow. Swallowing and talking become more complicated, that may lead to choking. Chorea gets worsened with the progression of the disease. The proximal group of muscles and axial trunk muscles are affected consecutively, while the intensity and amplitude of these uncontrolled movements are increased instantaneously. Chorea further results in secondary problems in daily life, for example, unstable walking, progressing imbalance, frequent risk of falling, breathing disturbances, dysarthria, dysphagia and speech difficulty. As the disease gets advanced, chorea may decline and get replaced by rigidity and parkinsonian like features.

Bradykinesia/ Akinesia

Uncontrolled slowing of both voluntary and involuntary movements is called bradykinesia and is usually combined with dystonia. Akinesia is the inability to start a specific action. The combination of dystonia and bradykinesia contributes to a high risk of falling. The situation of the subject usually gets worsened as the motor dysfunction is usually accompanied by other clinical manifestations such as impaired cognitive functions, neuropsychiatric deficits and postural deformity.

Eye movements

The pathological findings of eye movements remain the first symptom in the early stages of Huntington's disease and can be described to premanifest Huntington's disease gene carriers. Hence, more attention should be paid towards younger people during the examination of the eye movements. The clinical examination can be accompanied by vestibulo-oculography to objectify the findings and illustrate subclinical alterations. Incomplete suppression of optokinetic nystagmus is one of the first findings in the early stages of Huntington's disease. Moreover, the slowing of saccade velocity and delay in initiating volitional saccades were also seen (Reetz et al., 2015).

Behavioural and psychiatric signs and symptoms

Psychiatric symptoms occur in the early stages of the disease before the onset of motor symptoms. These symptoms usually have a detrimental effect on the daily life of the individual and their fam-

ily. Depression could be the most recurrent in this disease. Obsessions and compulsions disturb the patient's quality of life, leading to increased aggressiveness and irritability. Irritability is the most frequently occurring initial sign, during all the stages of this disease. Hypersexuality causes severe problems in the early stages of the disease while in later stages, it turns into hypo sexuality leading to relationship disturbances (Semaka et al., 2006). Cognitive decline is the other vital sign of Huntington's disease. Patients with Huntington's disease lose the capability of distinguishing relevant and irrelevant things and things to be ignored. These cognitive changes result in loss of flexibility of mind, inability to make mental adjustments, misjudgments, inability to organize, cognition impairment and all the psychomotor processes of the individual becomes severely diminished (Raymund, 2010).

Secondary signs and symptoms

Weight loss has been reported in all the patients from the early stages of disease onset. Loss of hypothalamic neurons results in decreased appetite, difficulty in talking and swallowing food and decline in function. Attacks of profuse sweating occur due to autonomic disturbances and circadian rhythm. Sleep disturbances can also be observed in these patients (Telenius et al., 1993).

Signs & Symptoms of Juvenile Huntington's Disease

When the first signs and symptoms of Huntington's disease begin before 20 years of age, the disease is called Juvenile Huntington's disease. The key characteristics of Juvenile Huntington's disease are learning and behavioural disturbances. Chorea is rarely seen in the first decade, and it appears prominently in the second decade. Epileptic fits are predominantly observed. Father is the affected parent in 75% of the juveniles (Quarrell et al., 2009).

DIAGNOSIS

The diagnosis of Huntington's disease is primarily based on clinical signs and symptoms. It is a prerequisite to collect, precise medical history followed by detailed family history. The diagnosis of the subjects might become difficult when parents are not known or have died due to some other reasons. In such instances, the medical records and autopsy reports of the patients must be taken into consideration. Motor changes with/without psychiatric or cognitive changes are the primary clinical characteristics required for diagnosis. Imaging, blood

tests or other diagnostic tests are found to be of no significance in diagnosis. Chromatography is used to record chorea accurately and objectively. Many studies are being conducted to study the changes in brain functioning and imaging before the onset of the clinical manifestations (Henley *et al.*, 2009).

According to the review conducted by the Johannes Schiefer, the total motor score (TMS) of the Unified HD Rating Scale (UHDRS) was considered as the gold standard in therapeutic and observational studies due to its accuracy and its convenience in assessing motor symptoms. However, TMS does not found to be the most appropriate assessment to illustrate these rare changes in premanifest HD like dystonia, chorea, disturbances in eye movements and minimal changes in the gait and balance. Various new motor assessment tests have been developed, aiming at the objective of accuracy based on computerized tools called Q-motor tests. These sensitive Q-motor tests were established by investigating the variability of tongue protrusion force of the subject at different levels, and both speeded and metronome-related finger tapping. These Q motor tests are being used successfully in large observational trials.

According to a clinical review performed by Raymond ACR, DNA determination of Huntington gene on chromosome 4 showing at least 36 CAG repeats is considered as the gold standard for diagnosis (Jankovic and Roos, 2014). Clinical triad has a significant role in the diagnosis of Huntington's disease. The triad includes chorea, cognitive and psychological disturbances. The first step in diagnosing cognitive impairment is cognitive screening tests. Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment Test (MoCA) are used in assessing cognitive performance. MoCA is found to have higher sensitivity when compared to MMSE. Most of Huntington's disease centres are using more comprehensive neuropsychological test battery of UHDRS which accurately diagnoses cognitive and psychiatric disturbances using symbol digit modality test, stoop colour word test and verbal fluency test. Mild cognitive impairment describes the transitional stage between dementia and normal cognition—the decline in cognition increases as the disease progresses (Paulsen and Long, 2014).

MANAGEMENT

Pharmacological

The pathogenesis of Huntington's disease is still unrevealed, and there is no treatment available for the cure of the disease. Though there were many drugs of choices available for symptomatic treatment aiming to improve the quality of life in the

patient, it is not always a pre-requisite to treat all the signs and symptoms of the patient. The individualization of drug therapy is based on clinical symptoms and quality of life of the patient. The initiation of symptomatic medication has no direct effect on the neurodegenerative process; therefore, the treatment must be typically based on the patient's needs. The pharmacological effects and side effects of the treatment must be monitored regularly (Armstrong and Miyasaki, 2012; Reilmann, 2013).

Depressive symptoms in Huntington's disease respond well to pharmacologic therapy. In a small study conducted for evaluating depression scores, venlafaxine was found to be effective though it produces unpleasant side effects such as nausea and irritability. Mirtazapine can be considered as an alternative in patients suffering from severe depression and sleep disturbances. SSRI's can also be used in treating the depression in these patients. Risperidone, olanzapine, ziprasidone, aripiprazole, quetiapine are the most frequently prescribed drugs for treating chorea, as these drugs produce minimal side effects when compared to classic neuroleptics. Benzodiazepines, (particularly lorazepam) are the right drug of choice for managing agitation. According to a retrospective study conducted in 2008, Risperidone improved the psychiatric functioning in these patients. Clozapine can be recommended in the conditions of severe psychosis, as it will not cause extrapyramidal symptoms, but the blood count must be regularly monitored. Depression and apathy are the two conditions often co-exist, and Methylphenidate or dextroamphetamine can be prescribed in treating primary apathy. SSRIs, benzodiazepines and non-benzodiazepines are commonly used in treating anxiety agitation and sleeping disorders. Severe or refractory symptoms are usually treated with atypical antipsychotics, while SSRI's are recommended for obsessive-compulsive symptoms (Squitieri *et al.*, 2001).

Non-Pharmacological

The non-pharmacological therapy for managing Huntington's disease includes physiotherapy, speech therapy and psychotherapy. The physiotherapist instructs appropriate and safe exercises to the patient, which enhances the strength, flexibility, balance and co-ordination. Though these exercises do not aid in curing the disease, these help in maintaining mobility and reduce the risk of fall. To reduce the severity of locomotory problems, proper instructions on the use of supports to improve posture is required. Huntington's disease significantly impairs the muscles involved in speech, eating and

swallowing. A speech therapist helps in improving the ability to speak by using appropriate communication devices. Psychiatrist counsels the patient in managing behavioural problems, facilitates effective communication among family members, thus helps in maintaining a healthy relationship (Nance *et al.*, 2012).

CONCLUSION

The advances are made in discovering mutations that cause Huntington's disease. Therapeutic options are still limited to symptomatic treatment and supportive care. The progression of the disease leads to more dependency affecting a patient's quality of life which impacts the entire family and social environment. Thus along with the pharmacotherapeutic approach, special emphasis has to be laid on non-pharmacological treatment that helps in substantial gaining of motor function at varying degrees. At a therapeutic setting, all the needs of the patients are to be addressed as the advancement in the development of new therapeutic agents are paving the way for the better outcomes in the management of Huntington's disease and thereby promising better healthcare for these patients.

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Conflict of Interest

The authors declare no conflicts of interest.

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