

## Huntington's Disease-A Review



**Venkateswara Rao P<sup>1</sup>, Rohini P<sup>2</sup>, Bhagyasree P<sup>3</sup> and SDVS Kiran<sup>1\*</sup>**

<sup>1</sup>Professor & Principal, St. Mary's College of Pharmacy, India

<sup>2</sup>University college of Pharmaceutical Sciences, AcharyaNagarjuna University, India

<sup>3</sup>Research Scholar, University college of Pharmaceutical Sciences, AcharyaNagarjuna University, India

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**\*Corresponding author:** SDVS Kiran, Professor & Principal, St. Mary's College of Pharmacy, India Global Pharmacovigilance, MSN Labs, India, Tel: 9908732605; Email: sdvskiran@gmail.com

### Abstract

Huntington's disease (HD) was first identified and described by George Huntington Huntington's Disease. (HD) is a progressive neurodegenerative disorder that gradually declines cognitive skills, impair memory and normal movements of affected individuals. HD affects most commonly the basal ganglia which are a group of nerve cells at the base of the brain. The basal ganglia are involved in various functions including control of voluntary motor movements. Finally in 1993, the researchers discovered a trinucleotide repeated chain (CAG) which was unstable. Now days there are promising research ideas which may lead to a concrete cure. With increased ideas and further understanding of the molecular level of the pathology, the previously unresolved "dancing disorder" may be closer to a cure than ever before. The developments are promising, but one thing is certain: the road to a solution is a long one.

**Keywords:** Huntington's disease (HD); Trinucleotide chain; CAG; Cognitive skills

### Introduction

Huntington's disease is an autosomal dominant disorder which usually begins in mid-life and is characterized by a progression of psychological change and dementia. Huntington's disease consists of a genetic mutation which manifests itself in the form of loss of motor control and cognitive decline. Huntington's disease is a dominant autosomal mutation, so if an individual person has Huntington's disease, his or her children have 50% chance to inherit the mutant gene and if one copy of the mutated gene is present, the symptoms will appear [1]. HD affects most commonly the basal ganglia which are a group of nerve cells at the base of the brain. The basal ganglia are involved in various functions including control of voluntary motor movements. The main components of the basal ganglia are the dorsal striatum comprising of caudate nucleus and putamen, ventral striatum comprising of nucleus accumbens and olfactory tubercle, globuspallidus, ventral pallidum, substantianigra and subthalamic nucleus.

### History

In 1872 Huntington's disease was first identified and described in a paper by George Huntington [1], granting a model for the disease's phenotypes [2]. His patients had a common lineage - all had family members which had emigrated from Suffolk, England in the mid-1600s. Before him, his father and grandfather also studied

the same group of patients [1]. It is believed that the occurrence of Huntington's disease was seen in 1600s, but it was misunderstood as a "dancing disorder" and was viewed as witchcraft [3]. Although it is believed that previous characterizations of people with Huntington's disease were recorded, the credit for the development of the disease characterization is still granted to George Huntington [4]. Even after his paper was published, it was over 100 years ago the gene associated with Huntington's disease was discovered [4]. In order to isolate this unknown gene, researchers used the DNA samples of families in Venezuela, where Huntington's disease and consanguinity are highly prevalent [4]. Finally in 1993, the researchers discovered a trinucleotide repeated chain which was unstable when expanded [4] and which they believed was strongly linked to Huntington's disease.

### Epidemiology

Huntington's disease is a rare neuropsychiatric disorder with a prevalence of 5-10/100,000 in the population. Genetic confirmation of the CAG repetition is the hallmark of epidemiological measure of HD. Prevalence studies incorporating both genetic and clinical diagnostic standards [5]. Germ line instability of intermediate alleles increases with CAG repeat length, indicating that longer CAG repeats in the general population results in higher CAG expansion rate and higher prevalence of HD.

### Pathophysiology

The most neuropathology in HD shows within the neostriatum, in which gross atrophy of the caudate nucleus and putamen is accompanied by selective neuronal loss and astrogliosis. Marked neuronal loss also is seen in deep layers of the cerebral cortex. Other regions, including the globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cerebellum, show varying degrees of atrophy depending on the pathologic grade [6].

Huntington's disease affects both cognitive and motor abilities. Patients experience chorea-over-the-top jerky movements which are uncontrolled. Due to these erratic movements, many see increased muscle tone, also called dystonia [4]. Often, the uncontrolled muscles begin with those farthest along the limbs from the trunk, i.e. fingers and toes, and those muscles in the face and tongue [7]. Memory, especially working memory, becomes severely limited. A loss of this type of memory is due to damage of the caudate nucleus and other subcritical areas. Nonetheless, damage to basal ganglia is reflected in the inability to follow procedural memory. Implicit memories are also lost, culminating in difficulty chewing and swallowing. However, long term memory is still available, and episodic memories, with prompting, can still be accessed [1]. Cognitive speed, inability to concentrate, trouble processing problems to come to a solution, and spatial functioning are all impaired. It is harder for Huntington's disease patients to initiate behaviours, yet once started, they become fixated on these behaviours, losing sight of other activities [1]. Additionally, between 13 and 71% of those with Huntington's disease also suffer from anxiety [8]. One study showed that about 34% of Huntington's disease patients experience changes in their anxiety [8]. No relationships seem to appear between anxiety and age or in gender [8]. A positive relationship is seen between anxiety and agitation, because of struggling relationships or because of both begins to manifest as a result of the onset of disease and the many upcoming and ongoing changes [8].

### Mitochondria enzymes

In biochemical studies defects in respiratory chain is found in HD individuals. The activity of complex II/III are greatly decreased in comparison of complex IV in HD patients but pre symptomatic patients has shown no changes in the activity of complex II, III and IV. Minor changes were observed in respiratory chain enzymes of cerebral cortex but no changes were observed in blood cells. The other enzymes of oxidative metabolism were also reported with reduced activity in the striatum. The levels of aconitase and pyruvate dehydrogenase complex were also significantly decreased in HD individuals. These decreased enzymes levels were observed in symptomatic patients having atrophy of striatum.

### Molecular understandings

The huntingtin gene is present on the short arm of chromosome four [1,8]. The huntingtin gene is believed to have a role in cell signaling as well as adenosine monophosphate as a binding protein and to help the body prevention of cell toxicity and cell death [9]. The wild type of gene is generally seen in the nervous system [10].

The protein has presence in the cytoplasm and vesicles of neuronal cells in the brain [3]. This specific gene codes for three cytosine-adenine-guanine (CAG) cycles that are repeated up to 27 times in a normal, wild type genome [1]. If an individual has between 36-40 repetitions, he/she has a chance of developing Huntington's disease. The mutation that occurs in Huntington's disease involves this trinucleotide cycle continuing to repeat unchecked 40 or more times which forms the mutant huntingtin protein [1] found in axon one of the gene [3]. The repeat occurs on the 5' end of the chromosome and the repetitive sequence is then translated into a polyglutamine (polyQ) region [4]. Dopamine, glutamate, and  $\gamma$ -aminobutyric acid are the main neurotransmitters affected by the disease [9]. The earliest areas affected by the brain are the striatum and sub-regions of the cortex [4] within the basal ganglia and cortex [9]. There is a severe loss of neurons in these areas [9]. Anticipation often occurs in the transmission of a mutant huntingtin gene, where the child has more CAG repeats than the parent. This phenomenon is generally exhibited if the father passes down the disease [1]. Usually, children whose fathers have Huntington's disease may see symptoms in themselves about 10 years earlier than the father did [4].

### Aetiology

Huntington's disease is an autosomal dominantly inherited disease caused by an prolonged CAG repeated chain on the short arm of chromosome 4p16.3 in the Huntingtin gene [11]. This gene codes as the huntingtin protein and, on axon 1, contains the CAG line. The wild-type contains a CAG repeat, coding for a polyglutamine stretch in the protein at that site in the range 5 to 25. Huntington's disease is associated with 36 repeats or more. Definite clinical manifestation will occur if the number of repeats exceeds 40. The range 36-39 leads to an incomplete penetrance of the disease or to a very late onset. The range between 29 and 35, the so-called intermediate alleles, is unstable, which means that these alleles are prepared for the change during reproduction. Copying the gene may leads to mistake and very often they lead to elongation and shortening. This phenomenon is mainly seen in the males [12]. An inverse correlation has been described between the length of the repeat and the age. The longer the CAG is repeated, the earlier is the onset. When the disease starts before the age of 20 years, so-called juvenile Huntington's disease (JHD), the repeat often exceeds 55 [13]. The length of the repeat determines about 70% of the variance in age at onset and gives no indication at all about the initial symptom, the course, or the duration of illness. The only correlation shown is the faster weight loss associated with a longer CAG repeat [14]. The normal wild-type Huntingtin protein plays a role in synaptic function and is possibly protective against the toxic mutant. [15]. There is evidence that the mutant form leads to a gain of function as well as there is a loss of function. The role of the mutation has been studied in many models: cells, fibroblasts, *C. Elegans*, *Drosophila*, mice, rat, sheep and monkey. Mice models (more than 10 available) are most commonly used. [16,17] The selective neuronal dysfunction and subsequent loss of neurons in the striatum, cerebral cortex, and other parts of the

brain seen in the cases of HD. Several mechanisms of neuronal cell death have been proposed for HD, including:

- a) Excitotoxicity.
- b) Oxidative stress.
- c) Impaired energy metabolism.
- d) Apoptosis.

### Excitotoxicity

Excitotoxicity refers to the neurotoxic effect of excitatory amino acids in the presence of excessive activation of postsynaptic receptors. NMDA receptors are depleted in the striata of patients with HD, suggesting a role of NMDA receptor-mediated excitotoxicity, but no correlation exists between the distribution of neuronal loss and the density of such receptors.

### Oxidative stress

Oxidative stress is caused by the presence of free radicals (i.e. highly reactive oxygen derivatives) in the large amounts. This may occur as a consequence of mitochondrial malfunction or excitotoxicity and can trigger apoptosis. Striatal damage induced by quinolinic acid can be ameliorated by the administration of spin-trap agents, which reduce oxidative stress, providing indirect evidence for the involvement of free radicals in excitotoxic cell death.

### Impaired energy metabolism

Impaired energy metabolism reduces the threshold for glutamate toxicity and can lead to activation of excitotoxic mechanisms as well as increased in the production of reactive oxygen species. A reduction in the activity of the respiratory chain complex II and III (complex IV) of mitochondria of caudate neurons in patients with HD.

In rats, intrastriatal injections of 3-nitropropionic acid (3-NP), an inhibitor of succinate dehydrogenase or complex II of the respiratory chain, cause dose-dependent in ATP depletion which was increased in lactate concentration, and neuronal loss in the striatum. Systemic injections of 3-NP into rats produce a selective loss of medium spiny neurons in the striatum.

### Apoptosis

Apoptosis is the cell death that is activated normally in the nervous system during embryogenesis to remove supernumerary neurons as part of natural development. Morphological features of apoptosis have been well characterized. Oxidative stress, excitotoxicity, and partial energy failure can lead to apoptosis. A subset of neurons and glia in the neostriata of patients with HD appears to undergo apoptosis; one theory is that expanded polyglutamine repeats cause neuronal degeneration through abnormal interactions with other proteins containing short polyglutamine tracts [18,19].

### Juvenile Disease

As mentioned above, when the CAG repeating region is extremely long, Huntington's disease may occur in juveniles. If the polyQ region is greater than 50 or 60 glutamines, a juvenile form of the disease is experienced, with many different symptoms than the general disease symptoms [4,20]. When Huntington's disease symptoms develop in a person before age 20, it is considered Juvenile Huntington's disease. If the person has not reached to age 10, it is considered as childhood-onset [20]. The youngest person who develops the symptoms of Huntington's disease was two years old [4]. When Huntington wrote his paper about Huntington's disease; he has not reported any cases on juvenile onset. Whereas in 1863, JW Lyon had already published a paper on which is now called as Juvenile Huntington's disease and soon after Huntington's reported in 1872 A. Harbinson published the first report of childhood-onset of Huntington's disease [20], so it has been known about for many years. When a juvenile develops in Huntington's disease, the father is the parent with the disease. During spermatogenesis, the CAG repeated length becomes less stable, so the length increases to the level which raises the juvenile disease [20]. Juvenile patients also suffer from seizures and bradykinesia, a retardation of body movements [4]; they usually do not develop chorea [20]. The brain experiences deterioration in the cerebellum, hypothalamus, thalamus, frontal cortex, and hippocampus.

### Symptoms [21]

Huntington's disease usually causes movements, cognitive and psychiatric disorders with a wide spectrum of signs and symptoms. Which symptoms appear first varies greatly among affected people. During the course of the disease, some disorders appear to be more dominant or have a greater effect on functional ability.

### Movement disorders

The movement disorders associated with Huntington's disease can include both involuntary movement problems and impairments in voluntary movements. Such as:

- a) Involuntary jerking or writhing movements (chorea).
- b) Muscle problems, such as rigidity or muscle contracture (dystonia).
- c) Slow or abnormal eye movements, Impaired gait, posture and balance.
- d) Difficulty with the physical production of speech or swallowing.

### Cognitive disorders

Cognitive impairments often associated with Huntington's disease include:

- a) Difficulty organizing, prioritizing or focusing on tasks.
  - b) Lack of flexibility or the tendency to get stuck on a thought.
  - c) Behaviour or action (perseveration).
  - d) Lack of impulse control that can result in outbursts.
  - e) Acting without thinking and sexual promiscuity.
  - f) Lack of awareness of one's own behaviours and abilities.
  - g) Slowness in processing thoughts or "finding" words.
  - h) Difficulty in learning new information.
- b) Changes in fine motor skills that might be noticeable in skills such as handwriting.
  - c) Tremors or slight involuntary movements.
  - d) Seizures.

### Causes

Huntington's disease is caused by an inherited defect in a single gene. Huntington's disease is an autosomal dominant disorder, which means that a person needs only one copy of the defective gene to develop the disorder. With the exception of genes on the sex chromosomes, a person inherits two copies of every gene i.e. one copy from each parent. A parent with a defective gene could pass along the defective copy of the gene or the healthy copy. Each child in the family, therefore, has 50% of chances in inheriting the gene which causes the genetic disorder. Common causes of death include:

- a) Pneumonia or other infections.
- b) Injuries related to falls.
- c) Complications related to the inability to swallow.

### Treatment

At present, there is no cure for Huntington's disease; therefore physicians generally focus on treating the various symptoms associated with the disease [9]. From the above knowledge, knowing about the gene and the mutation should allow for significant studies and development of treatments [10].

### Medications for movement disorders [22]

Drugs to treat movement disorders include the following:

- a) Tetrabenazine: Is specifically approved by the Food and Drug Administration (FDA) to suppress the involuntary jerking and writhing movements (chorea) associated with Huntington's disease. A serious side effect is the risk of worsening or triggering depression or other psychiatric conditions. Other side effects include drowsiness, nausea and restlessness.
- b) Antipsychotic drugs: Such as haloperidol and chlorpromazine have a side effect of suppressing movements. Therefore, they may be beneficial in treating chorea. However, these drugs may worsen involuntary contractions (dystonia) and muscle rigidity. Other drugs, such as risperidone and quetiapine, may have fewer side effects but still should be used with caution, as they may also worsen symptoms.

Other medications that may help to suppress chorea which include amantadine, levetiracetam and clonazepam. At high doses, amantadine can worsen the cognitive effects of Huntington's disease. It may also cause leg swelling and skin discoloration. Side effects of levetiracetam include nausea, stomach upset and mood swings. Clonazepam may also worsen the cognitive side effects of Huntington's disease and causes drowsiness. It also has a high risk of dependence and abuse [23].

### Psychiatric disorders

The most common psychiatric disorder associated with Huntington's disease is depression. Signs and symptoms may include:

- a) Feelings of irritability.
- b) Sadness or apathy.
- c) Social withdrawal.
- d) Insomnia.
- e) Fatigue and loss of energy.
- f) Frequent thoughts of death.
- g) Dying or suicide.

Other common psychiatric disorders include:

- a) Obsessive-compulsive disorder\_ a condition marked by recurrent, intrusive thoughts and repetitive behaviours.
- b) Mania\_ which can cause elevated mood, over activity, impulsive behaviour and inflated self-esteem.
- c) Bipolar disorder\_ a condition with alternating episodes of depression and mania.

In addition to the above symptoms, weight loss is common in people with Huntington's disease, especially as the disease progresses.

### Symptoms of juvenile Huntington's disease

The starting progression of Huntington's disease in young people may be slightly different from that in adults. Problems often present in themselves early in the course of the disease include:

#### Behavioural changes:

- a) Loss of previously learned academic or physical skills
- b) Rapid and significant drop in overall school performance
- c) Behavioural problems.

#### Physical changes

- a) Contracted and rigid muscles that affect gait (mostly in young's).

## Medications for psychiatric disorders

Medications to treat psychiatric disorders will vary depending on the disorders and symptoms. Possible treatments include the following:

- a) Antidepressants: include such drugs as citalopram, escitalopram, fluoxetine and sertraline. These drugs may also have some effect on treating obsessive-compulsive disorder. Side effects may include nausea, diarrhoea, drowsiness and low blood pressure.
- b) Antipsychotic drugs: such as quetiapine, risperidone and olanzapine these drugs may suppress violent outbursts, agitation, and other symptoms of mood disorders or psychosis.
- c) Mood-stabilizing drugs that can help prevent the highs and lows associated with bipolar disorder include anticonvulsants, such as evaporate, carbamazepine and lamotrigine [24].

## Future Perspectives

HD is a physically, psychologically and socially devastating neurological disorder knowing about the disease and care for patients has increased now a days. Huntington's disease is a lifelong disease for both the individual and the family. From the moment the gene was localised in 1983, and particularly after 1993, attention has focussed on the pathophysiological pathway with the aim of developing a therapy. It was the first autosomal dominant disease where diagnosis became possible and it was the first trinucleotide disease to be described about CAG. Consequently, since from 1993 many researchers has shown interest on this disorder. The number of publications has increased enormously. The basic studies mainly focus on the pathophysiology and the search for biomarkers. A better understanding of the pathophysiology will surely lead to drug development to interfere in the pathological process. The second issue is the search for reliable, early to detect and clinically relevant markers for onset of the end course of the disease. In parallel with the rational pathway to find solutions to treat this disorder, attention is being paid to find the best care for all the patients and at high risk persons at this point in time. The developments are promising, but one thing is certain: the road to a solution is a long one.

## Summary

HD now affects thousands of individuals. HD has a late onset which severely affects motor and cognitive function. It is passed down from parent to child and only one mutated gene is present when an individual develops the disease. Most symptoms are not able to be detected until midlife, though many mental and emotional deficits are present prior to physical onset. The progression of the disease lasts about 20 years. Jerky movements, irritability, depression, and motor decline are all symptoms to be expected when one is suffering from Huntington's disease. Very rarely does one develop the juvenile onset of the disease, which consists of a longer CAG repeat sequence than the adult disease. When onset is earlier, the symptoms are much more severe, and

death may occur much sooner. Though there is no cure, there are some different treatments available to help aid in the severity of symptoms. Yet, there are promising research ideas which may lead to a concrete cure. With increased ideas and further understanding of the molecular level of the pathology, the previously unresolved "dancing disorder" may be closer to a cure than ever before.

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