



Huntington's Disease: Clinical Complexities and Therapeutic Strategies

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ABSTRACT

Named after physician George Huntington, Huntington's disease (HD) is an adult onset, rare, progressive, fatal, neurodegenerative autosomal dominant disorder, clinically characterized by abnormal movements, dementia, and psychiatric syndromes. The mechanisms by which neuronal degeneration and cell death are being generated in HD may include excitotoxicity, energy deficit, oxidative stress, inflammatory processes, and protein aggregation. Genetically, HD is caused by expanded CAG repeat in the Huntington gene which encodes an abnormally long polyglutamine repeat in the Huntington protein. HD share several of feature of other neurodegenerative disorders like delayed onset, selective neuronal vulnerability, abnormal protein aggregation and processing and cellular toxic effects involving both cell autonomous and cell cell interaction. In the brain, the basal ganglia (caudate and the putamen) is highly affected which organize muscle-driven movements of the body or motor movement. The disease is characterized by a primary progressive loss of medium spiny projection neurons within the basal ganglia. Unfortunately, there is no cure. Management should be multidisciplinary and is based on treating symptoms with a view to improving quality of life. Chorea is treated with dopamine receptor blocking or depleting agents. Medication and non-medical care for depression and aggressive behavior may be required. The progression of the disease leads to a complete dependency in daily life, which results in patients requiring fulltime care, and finally death. The most common cause of death is pneumonia, followed by suicide.

Keywords: Huntington's disease, Chorea, Apathy, motor abnormalities.

1. INTRODUCTION

The first description by Waters, of a patient with what we now call Huntington's chorea, dates from 1842. But it was not until 1872, after the lecture and description of the disease by George Huntington, that it became known as Huntington's chorea. Although George Huntington was not the first person to describe the condition, his was the first clear, succinct account.

George Huntington (1850-1916) presented his findings before the Meigs and Mason academy of medicine at Middleport, Ohio on 15 February 1872 and published it only two month later in Philadelphia Journal, The Medical and Surgical Reporter [1]. Initial development in this area arose from the illness of Woody Guthrie, the American folk singer, who developed HD symptoms around 1952 and died in 1967 at the age of 55. His widow Marjorie devoted the later part of her life for promoting all aspects of HD [2]. For many decades its name remained unchanged, until the nineteen-eighties when, fully aware of the extensive non-motor symptoms and signs, the name was changed to Huntington's disease. In 1983, a linkage on chromosome 4 was established and in 1993 the gene for HD was found [3].

HD passes within families from generation to generation with onset in middle age and characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia [4]. Death occurs an average of 15 to 20 years after symptoms first appear, with some patients dying earlier from falls or suicide and others surviving for 30 to 40 years. Clinically detectable signs or symptoms usually begin between the ages of 35 and 50, with death typically following 15-20 years later [5].

If the first symptoms and signs start before the age of 20 years, the disease is called Juvenile Huntington's disease (JHD). Behavior disturbances and learning difficulties at school are often the first signs. Motor behavior is often hypokinetic and bradykinetic with dystonic components. Chorea is seldom seen in the first decade and only appears in the second decade. Epileptic fits are frequently seen. The CAG repeat length is over 55 in most cases. In 75% of the juveniles the father is the affected parent [6].

2. EPIDEMIOLOGY

HD is a neurodegenerative disorder for which there is currently no effective therapy [7]. The prevalence of the clinical syndrome is 3-7: 100000 whereas nearly 20: 100000

are carriers of the gene responsible for the disease. Symptoms include weakening of mental abilities leading to a change in personality (i.e., depression, suicidal tendencies, and in rare cases, violent behavior), development of dementia, loss of psychomotor functions, coordination, and abnormal sudden jerky involuntary movements collectively called chorea that heavily affect gait and agility [8].

HD is currently found in many different countries and ethnic groups around the world. There are varying rates of prevalence in different racial groups [9]. The highest frequencies of HD are found in Europe and countries of European origin. The lowest frequencies are documented in Africa, China, Japan, and Finland.

The frequency of HD in different countries varies greatly. A few isolated populations of western European origin have an unusually high prevalence of HD. These include the Lake Maracaibo region in Venezuela (700 per 100,000 people), the island of Mauritius off the South African coast (46 per 100,000 people), and Tasmania (17.4 per 100,000 people). The prevalence in most European countries ranges from 1.63-9.95 per 100,000 people [10]. A study on the distribution of C-A-G repeats in the normal population suggests a higher prevalence of HD in India closer to that seen in Western Europe. Based on the results, haplotype analysis suggested the presence of a founder mutation in a subset of families and provide evidences for multiple and geographically distinct origins for HD mutation in India [11].

3. PATHOBIOLOGY OF HD

The part of the brain most affected by HD is a group of nerve cells at the base of the brain collectively known as the basal ganglia. The basal ganglia organize muscle-driven movements of the body, or “motor movement” [12]. The major components of the basal ganglia are the caudate and the putamen (together known as the striatum) and the globus pallidus (external and internal regions). The clinical symptoms of HD reflect the pattern and extent of neuronal loss within different components of the basal ganglia-thalamocortical circuit. The neostriatum (caudate nucleus and putamen) receives excitatory glutamatergic inputs from the entire neocortex, the first step in the anatomical loop responsible for the initiation and execution of movement [13]. The GABAergic basal ganglia output projections to the thalamus maintain a tonic inhibition of their target nuclei, which is modulated by two opposing pathways (direct and indirect) which integrate the input and output compartments within the basal ganglia [14]. It is an imbalance in the relative contributions of these two regulatory pathways which triggers and dictates the nature of the motor dysfunction in HD.

In contrast, in indirect pathway, striatal efferents containing GABA and enkephalin (GABA/ENK) project [15]. Disruption of these pathways in HD leads to motor dysfunction. In HD there is preferential loss of indirect pathway resulting in “disinhibition” of the thalamus is manifested by the development of involuntary choreic movements. In contrast, it is proposed that the rigid akinetic state seen in some HD patients results from the additional loss of striatal GABA/SP efferents projecting directly to the globus pallidus internal (GPi). There is also recent evidence that the dyskinesia seen in HD patients is influenced by imbalances between neuronal activities within the basal ganglia internal and external pallidal segments, as well as between the segments [13].

3.1. Susceptibility of striatal and cortical nerve cells in HD

The huntingtin protein (HP) is present in all the cells of the body, not just nerve cells. We do not know the exact details of the function of the normal huntingtin protein in the body, but we know that huntingtin is necessary for development and is active throughout the body. However, HP does not kill all the cells in the body; rather it selectively kills nerve cells. The studies on HD suggest that the HP regularly interacts with proteins found only in the brain and that the altered form of the huntingtin protein disrupts this interaction, leading to nerve cell death [16, 17].

HP interacts with two proteins: huntingtin’s interactor protein (HIP-1) and huntingtin’s associated protein (HAP-1). These two proteins are present only in the brain and this finding could explain why HD only affects the brain even though the HP is present throughout the body. The number of C-A-G repeats in the huntingtin gene determines how the huntingtin protein interacts with HIP-1 and HAP-1. As repeat numbers increase, huntingtin binds less to HIP-1 and more to HAP-1. Much information about how these proteins interact and what these interactions have to do with HD are yet to be discovered [18].

The striatum is composed of a variety of medium to large neurons that differ in their size and dendritic profile as well as neurochemical content and output. Severe loss of medium sized striatal neurons was seen in the HD brain. Medium spiny neurons are inhibitory projection neurons carrying the output of the striatum to the globus pallidus and the substantia nigra and are the major neuronal type, comprising approximately 95 percent of the neuronal cells in the striatum. They have large dendritic tree and use GABA as their neurotransmitter [19].

As these neuron degenerate in HD, the neurochemical they contain, including glutamic acid decarboxylase (GAD), substance-P, enkephalin, calcineurin, calbindin, adenosine receptors and dopamine receptors, also decrease. The medium

spiny neurons are subdivided into two groups according to their connectivity and neurochemical difference. Medium spiny neurons that express the D1 dopamine receptors and substance P project to GPi and SNc, where those expressing D2 and enkephalin project to GPe. Both subpopulations of medium spiny neurons degenerate in HD, but several studies have shown that the two types of projection neurons are differentially affected in the course of the disease [19, 20].

Numbers of theories have been presented, to determine the exact events involved in the progression of cell deaths caused by HD. One theory proposes that neurons die in HD because of an over-accumulation of normal excitatory chemicals involved in nerve impulses. One of the neurotransmitters released by the basal ganglia is called glutamate, which acts as an excitatory neurotransmitter in the brain. Excitatory neurotransmitters are normally present in the brain, but, if they are released in excessive amounts or if brain cells are weak, these excitatory chemicals can cause cell damage and become chemicals known as "excitotoxins." [21] This first theory had to be modified when high levels of glutamate were not found in the brains of all HD patients. The modification has to do with that the mitochondrial dysfunction play a role in pathogenesis of HD. Mitochondria - a type of organelle that produces energy in animal cells. The mitochondria of striatal cells may be damaged with the onset of HD. Scientists today believe that the damaged mitochondria of people with HD make striatal cells unable to produce as much energy as they need, which then makes the cells more susceptible to normal levels of glutamate [22].

Another theory to explain the death of nerve cells postulates that the cells actually kill themselves in response to chemical changes caused by HD. HD triggers the early death of neurons by accelerating a normal process called apoptosis [16-23].

It is also reported that activity of caspases which initiate apoptosis is increased in the HD brain [24]. To sum up, the neurobiological effects of HD appear to be the result of a number of different changes that ultimately go out of control. Many studies have shown that neurodegeneration is not confined to the basal ganglia but also occurs widely in cortical and other sub cortical regions [25].

4. NEUROPSYCHOLOGICAL AND CLINICAL VIEW OF HUNTINGTON'S DISEASE

Huntington's disease damages specific areas of the brain resulting in movement difficulties as well as cognitive and behavioural changes. Behavioural changes are a characteristic feature of HD and are often the most distressing aspect of the condition for individuals and families dealing with HD [26]. Other less well-known, but prevalent and often debilitating

features of HD include unintended weight loss, sleep- and circadian rhythm disturbances and autonomic nervous system dysfunction. The progression of the disease leads to more dependency in daily life and finally death. The most common cause of death is pneumonia, followed by suicide [27]. The brief descriptions of motor and behavioral symptoms in HD are described here.

4.1. Motor symptoms in HD

The movement disorder of HD consists of two components: involuntary movements and abnormal voluntary movements. Chorea, or choreoathetosis, is the movement abnormality most frequently associated with HD. It consists of continuous and irregular jerky or writhing motions. Disturbances of voluntary movement, however, are more highly correlated with functional disability and disease severity, as measured by the degree of brain disease. The disordered voluntary movements observed in HD include the following: abnormal eye movements, such as slow, hypometric saccades and catchy pursuit; uncoordinated, arrhythmic, and slow fine motor movements; dysphagia and dysarthria; rigidity; and gait disturbances.

The nature of the motor symptoms changes over time. The onset is usually insidious. Early complaints include clumsiness, difficulty with balance, and jerky movements or tremor. In addition to limb and truncal movements, patients may have motor tics or chorea involving respiratory, laryngeal, pharyngeal, oral, or nasal musculature. Chorea often plateaus and even wanes in the later stages of the disease, but disturbances in voluntary movement continue to progress [28].

The characteristic motor changes are involuntary, unwanted movements. Initially, the movements often occur in the distal extremities such as fingers and toes, but also in small facial muscles. In daily life, walking becomes unstable and the person can look as if he/she is slightly drunk. Gradually the unwanted movements spread to all other muscles from distal to more proximal and axial. Choreatic movements are present all the time the patient is awake. No single pattern exists, but facial choreatic movements can lead to a continuous movement of facial muscles where for instance an eyebrow is lifted, an eye closed, the head is bent or turned while the tongue is protruded with the lips pouting. Talking and swallowing gradually become more problematic leading to choking at any time in some patients. In later stages the patient even becomes mute. Dysarthria and dysphagia become very prominent during the course of the disease. All patients develop hypokinesia, akinesia, and rigidity leading to a slower pace of all activities (bradykinesia: slowness of movement) and a severe hesitation in embarking on a movement (akinesia: difficulty in starting movements) [27].

4.2. Behavior and psychiatric symptoms and signs

Psychiatric symptoms are very frequently present in the early stage of the disease, often prior to the onset of motor symptoms. Because of their impact on daily life, these symptoms and signs usually have a highly negative impact on functioning and on the family [29]. The most frequently occurring sign is depression. The diagnosis is difficult because weight loss, apathy and inactivity also occur in HD. Usually there is low self esteem, feelings of guilt and anxiety. Apathy is related to disease stage, whereas anxiety and depression are not. Suicide occurs more frequently in early symptomatic individuals and also in pre manifest gene carriers. Around the time of the gene test and the stage when independence diminishes are the most risky periods for suicide. Anxiety also occurs frequently (34-61%), sometimes in relation to uncertainty about the start and or the course of the disease. Obsessions and compulsions can disturb the patient's life and also lead to irritability and aggression. Irritability is often the very first sign, in retrospect, but in fact occurs during all stages of the disease.

Apathy is one of the most common behavioural symptoms of HD characterized by indifference or lethargy [30]. The individual may seem to be uninterested in his or her surroundings and lose enthusiasm as well as spontaneity. A lack of motivation and loss of the ability to initiate conversation or activities also tends to occur in individuals suffering from apathy [31]. Apathy occurs mainly due to the disconnection between the caudate to the frontal lobes and limbic system which mainly control "emotions" of the brain.

Depression is often dismissed as an understandable reaction being diagnosed with HD. While a saddened mood is an understandable response to the life changes and loss of abilities resulting from HD. Depression occurs in HD due to alteration in neurotransmitters, the chemicals in brain that regulate moods [31].

G. Huntington drew attention to the increased frequency of suicide among those with HD. From the one survey reports of Wexler 1979, it is true that many people with HD talk about option of suicide if their situation becomes unbearable [26-31].

People suffering from HD may remain even tempered; others may lose the ability to control their emotions. Emotional volatility may be evident in increased irritability or episodes of explosiveness [30]. For others, rigidity of thinking causes the individual to focus on one particular request. This individual may become irritable, frustrated or aggressive if demands are not met. When the caudate nucleus has deteriorated, emotions are improperly regulated, causing an increase in feelings of frustration and irritability.

Following damage to the basal ganglia and the caudate nucleus, individuals with HD may become "stuck" on one idea or activity. Inflexible thoughts and behaviour may also make it difficult for an individual to change from one activity or idea to another or to deal with changes in routines. These behaviours are often associated with Obsessive-Compulsive Disorder (OCD). True OCD, however, is uncommon in HD patients. Another possible cause of repetitive behaviour is that legitimate needs of the individual are not being met. He or she may repeat a request in hopes of being understood [26].

An individual with HD experience anxiety and sometimes excess worry occurs over seemingly trivial matters. Anxiety, a behavioural symptom of HD, is characterized by nervousness, restlessness, fidgeting, shallow breathing, sweating, fear, and panic rapid heart-rate [30]. For individuals with HD, continual life changes as HD progresses can be a source of anxiety. Some individuals become anxious about social engagements because they are embarrassed about visible symptoms such as chorea [31]. However, physical brain changes caused by the disease itself may also cause excessive anxiety.

Hallucinations, delusions and mania are very rare behavioural symptoms of HD. Hallucinations involve seeing, hearing or experiencing things that are not real such as feeling bugs crawling on you, hearing voices etc. Delusions are defined as thoughts about unreal situations [32]. Mania is also a very rare symptom of HD, characterized by an irritable mood, overactivity, decreased need for sleep and impulsiveness. Mania can drastically upset daily routine. Sometimes a period of mania is followed by a period of depression referred to as Bipolar Disorder.

A very common behavioural symptom of HD is altered sexuality. Possible cause is that the delicate balance of hormones in the brain is disrupted by the progression of HD causing changes in behaviours regulated by hormone levels. Most commonly, people with HD suffer from a decreased sex drive. Increased sex drive and inappropriate sexual behaviour are less common alterations of sexuality resulting from HD [30].

The term "cognitive" refers to tasks of the brain that involve knowing, thinking, remembering, organizing and judging. Certain changes in cognitive abilities are characteristic of HD and can significantly impact the lives of individuals with this disease [33, 34]. Cognitive changes in the HD may be due to the disruption of striatal-frontal circuits. In their daily lives, people with HD often exhibit poor planning and judgment. They may appear impulsive and show an absence of forethought and their actions being governed by immediate rather than long term considerations.

5. MANAGEMENT INCLUDING TREATMENT

The most commonly used therapies in HD patients are symptomatic drug therapies and no therapy has been developed that effectively modifies disease progression [7]. Despite the fact that the pathogenesis of HD has still not been resolved and a cure is not available, many therapeutic options are available for treating symptoms and signs with a view to improving quality of life. Although many signs and symptoms can be treated, it is not always necessary to do so. The patient's limitations in daily life determine whether or not drugs are required. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms. Drug treatment is, therefore, individualized and based on expert opinion and daily practice. Treatment consists of drug prescription and non-medication advice.

5.1. Dopamine blocking or dopamine depleting medications

Abnormal movements in HD occur as a result of increased activity via the direct circuit and decreased activity via the indirect circuit, both mediated by dopamine. Logically blocking the effects of dopamine should reduce choreic movements. Traditionally, typical neuroleptics were used to treat chorea but severe side effects associated with treatment led many to discourage their widespread use. The atypical neuroleptic clozapine binds to dopamine receptors and blocks dopamine binding and subsequent signaling. When tested in a double-blind placebo-controlled clinical trial [35]. Clozapine was only effective in reducing dyskinesias in patients that had no prior exposure to neuroleptics. Higher doses were required for reasonable effectiveness and these high doses were poorly tolerated in most patients. Evidence from small open label series supports the use of other atypical antipsychotics in HD. These include olanzapine, risperidone, and aripiprazole [36].

Tetrabenazine is a drug that is available clinically in many countries which acts by preventing the packaging of dopamine into vesicles, thereby suppressing its presymptomatic release [37]. It also prevents dopamine signaling by blocking postsynaptic dopamine receptors. Drowsiness, depressed mood, parkinsonism, and akathisia were the most commonly reported adverse effects [38].

5.2. Glutamate antagonism- NMDA Receptor Antagonists

Excitotoxicity is the major cause of death of neurons in the HD. Increase in glutamate release activate the NMDA receptors and increase the level of Ca^{2+} and cause neurotoxicity. The drugs which block the NMDA receptors may be useful to decrease the symptoms of HD [39].

The moderate effectiveness of antidopaminergic therapies may be outweighed by debilitating side effects like Parkinsonism, tardive dyskinesias, and severe depression. An alternative strategy is to use NMDA receptor antagonists. It has been thought for some time that levodopa-induced dyskinesias in Parkinson's disease (PD) occur as a result of increased NMDA receptor sensitivity [40] and are reduced by treatment with NMDA receptor antagonists [41]. The fact that dyskinesias in PD are clinically similar to chorea seen in HD provided the theoretical framework that NMDA antagonists may be effective in reducing chorea in HD. Multiple daily doses of amantadine were successful in reducing dyskinesias by up to 56% [39]. Additionally, there were no serious side effects and no effect on cognition. A second NMDA antagonist, memantine, has also been tested in clinical trials for HD. Memantine may be preferred to amantadine because it has a longer half-life, allowing for once daily dosing. While memantine was effective in treating chorea, it did not have any effects on cognition or behavior [37].

GABAergic modulation: GABA an inhibitory neurotransmitter is decreased in the HD brain and cerebrospinal fluid. Indeed the GABA mimetic drugs and GABA transaminase inhibitors are also used in the clinical trial for the treatment of HD [36-42].

Cannabinoids receptor agonists: In the brain the cannabinoids and their receptors behave as neurotransmitters or neuromodulators in a variety of processes, such as the regulation of motor behaviour, cognition, learning, memory and antinociception. It is also reported that the cannabinoids receptors are destroyed in the basal ganglia [43] therefore the treatment with cannabinoids could be beneficial for HD [44].

Antioxidants: One component of excitotoxicity in HD is oxidative stress and antioxidants may therefore have therapeutic utility. A novel antioxidant, BN-82451 improved motor ability and survival and ameliorated neurodegeneration in R6/2 HD mice [45].

5.3. Developing novel therapies for Huntington's disease

Agents that inhibit mutant huntingtin aggregation: The huntingtin aggregates and inclusions play a major role in the pathogenesis of HD. Inhibit mutant huntingtin from aggregation would provide a way to prevent the progression of the disease. These direct aggregation inhibitors have been tested in various HD models such as cell culture, HD *Drosophila* and transgenic HD mice [46, 47].

Transglutaminase inhibitors: Transglutaminase (TGase) can use huntingtin as a substrate to cross-link huntingtin molecules. TGase activity was found to have increased in HD postmortem brains. TGase provides an additional mechanism for the

formation of aggregation of mutant huntingtin. This suggests that TGase might play a role in HD pathogenesis therefore, is a potential therapeutic target [47]. Cystamine is an inhibitor of TGase showed a small but significant neuroprotective effect with improvement of motor function, survival and loss of bodyweight [48].

Protease inhibitors: Huntingtin can be cleaved by proteases, including caspases, calpain, and aspartyl protease. Caspase and calpain-mediated partial cleavage of mutant huntingtin promotes huntingtin aggregation and cellular toxicity, inhibitors of huntingtin partial cleavage might have therapeutic values. Caspase inhibitors, z-VAD-fmk and z-DEVD-fmk, can prevent cleavage of huntingtin by caspases and reduce cytotoxicity caused by expanded polyglutamine tract [49]. Caspase inhibitor minocycline was able to inhibit huntingtin aggregation, retard disease progress and prolong the lifespan of HD mice. Protease inhibitors could reduce N-htt fragments and in turn, prevent or delay disease progression [50].

Neuroprotective approaches: Neuroprotective strategies are designed to modify disease progression based on the concept of neuronal preservation. It is likely that disease-modifying strategies will ultimately be a more powerful approach relative to symptomatic treatments. These therapies attempt to attenuate or delay the onset of symptoms by preventing cell death and preserving neuronal circuitry in vulnerable brain regions. Neuroprotective therapies can be delivered in a systemic fashion (when they are capable of crossing the blood brain barrier) or applied directly to the brain via neurosurgical procedures [7].

Coenzyme Q10 Targeting enzymes or cofactors that play a role in energy production theoretically could help reduce cell death. Coenzyme Q10 is a molecule in the electron transport chain that carries electrons from complex I and II to complex III [51]. By keeping electrons with the enzymes in the mitochondrial membrane, coenzyme Q10 reduces formation of reactive oxidative species and oxidative stress. Mitochondrial energy impairments plague brain cells in HD, resulting in neuronal death and dysfunction.

Creatine: Creatine has been hypothesized to be effective as a therapy for HD because it is capable of buffering ATP levels in cells. Mitochondrial enzymes, and therefore ATP production, are disrupted in HD brains. When creatine is ingested it is converted into phosphocreatine and stored. In the face of an energy deficit, phosphocreatine can donate its phosphate to ADP in the presence of creatinekinase, producing the high energy ATP molecule [52]. Creatine has been shown to be effective in diminishing motor and cognitive symptoms in the 3-NP toxin-induced rat model of HD [53]. Beside them trophic factors (BDNF, CNTF, GDNF) and neurorestoration (Stem cell) therapy is also applied.

6. CONCLUSION

Huntington's disease is a devastating neurological disorder without effective treatment. There is an urgent need for developing effective therapies for HD. Researchers are actively investigating possible effective therapies based on current understanding of the molecular pathology of HD. Much attention has been focused on screening for drugs that prevent aggregation of huntingtin with expanded polyglutamine tract. The other approach is to use recent advances in molecular biology of neurotrophic factors, neuronal tissue transplantation and cell engineering in HD therapeutic developments with the aim of retarding or reversing HD pathology. However, no therapy has been shown to combat all of the symptoms associated with the disease: cognitive, motor, and psychiatric. Additionally, a treatment would have to be either neurorestorative or neuroprotective which increase survival. Until the discovery of one therapy that can address the myriad of concerns in HD, combinations of factors that target individual aspects of the disease may have to be considered.

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