PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Review Article

Huntington's Disease: An Update

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ABSTRACT

Huntington's disease is a complex degenerative disorder that affects the central nervous system. Huntington's disease is an autosomal-dominant, progressive neurodegenerative disorder typically presents during mid-life with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioral abnormalities. HD is caused by an expanded CAG repeat in the gene that encodes the protein huntingtin on chromosome 4; this results in progressive atrophy of the striatum as well as cortical and other extra striatal structures. Since 1993, genetic testing has been available to confirm diagnosis in affected adults and for pre-symptomatic testing in at-risk individuals. The review aims majorly on these areas namely: History, etiology, symptoms, pathophysiology, treatment and other aspects of Huntington's disease.

Keywords: Huntington's disease history, pathophysiology, symptoms and treatment

INTRODUCTION

Huntington's disease (HD) is a rare, genetic, progressive and always incurable, neurodegenerative disorder characterized by degeneration of neurons in the striatum and cerebral cortex, which results in involuntary motor movements. HD is extremely disabling and overwhelming disorder that progressively damages and destroys a person's ability to think, move voluntarily, and functions independently.[1]Alternative name to Huntington's disease is Huntington's chorea. Huntington's disease is not curable and is eventually fatal. It is very much a familial incurable disorder, because of its inherited nature; the defective gene that causes Huntington's disease is passed on from parent to child (figure 2). The rate of disease progression and the age at onset vary from person to person. Adult-onset HD, with its disabling, uncontrolled movements, most often begins in middle age. Some individuals develop symptoms of HD when they are very young—before age 20 termed as "early-onset" or "juvenile" HD.[1,2,3]

HISTORY OF HD

Before the 19th century, some HD sufferers may have been thought to be possessed by spirits or persecuted as witches, and were shunned or exiled by society. The first very thorough treatment of chorea was presented by Thomas Sydenham (1624-1689), a British physician. The first thorough description of the disease was given by George Huntington in 1872, who was a medical practitioner of Pomeroy, Ohio, USA. The disorder was then named after him as Huntington's disease.[4] Today the term Huntington's (or Huntington) Disease is more commonly used than Huntington's chorea. In 1993, a collaborative group of investigators discovered the gene that causes HD. The research group isolated the precise causal gene at 4p16.3, making this the

How to cite this article: A Kaur; Huntington's Disease: An Update; PharmaTutor; 2014; 2(7); 47-53

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ISSN: 2347-7881

first autosomal disease locus found using genetic linkage analysis [4].Modeling the disease in various types of animals, such as the transgenic mouse developed in 1996, enabled larger scale experiments. As these animals metabolisms are faster and their lifespans much shorter than humans, results from experiments are received sooner and research can be performed more quickly. The discovery that mHTT fragments misfold in 1997 led to the discovery of the nuclear inclusions they cause. These advancements and discoveries have led to increasingly extensive research into the proteins involved with the disease, potential drug treatments, care methods, and the gene itself.[5]

EPIDEMIOLOGY

It is difficult to tell how common HD is in a population. According to the available information from population surveys the world distribution of Huntington's disease (HD) in most European populations, both Northern and Southern, show a relatively high prevalence (4-8 per 100,000), and that the disorder may also be frequent in India and parts of central Asia. HD is notably rare in Finland and in Japan, but data for Eastern Asia and Africa are inadequate. The disorder may have been underestimated in the American black population. Populations derived from recent European immigration show frequencies and origins of HD comparable to those expected from their own origins and expansion; there is no evidence to suggest that the HD gene has spread disproportionally and its selective effect may be close to neutral.[6]

RISK FACTORS FOR HUNTINGTON'S DISEASE

Huntington disease is caused by a genetic defect on chromosome 4. The defect causes a part of DNA, called a CAG repeat, to occur many more times than it is supposed to. Normally, this section of DNA is repeated 10 to 28 times. But in persons with Huntington disease, it is repeated 36 to 120 times. This leads to repeat expansion in the *HTT* gene encoding huntingtin protein, located on chromosome band 4p16.3. The normal function of huntingtin protein is unknown, but in patients with the defective *HTT* gene, mutant huntingtin protein accumulates in clumps within brain cells; gross atrophy of the caudate nucleus and putamen occurs with astrogliosis leads to cellular damage through alterations in various cellular pathways, including mitochondrial function[7].

TYPES OF HUNTINGTON'S DISEASE

There are two main types of Huntington's disease or Huntington's chorea; they are adult onset and early onset Huntington's disease. The word chorea refers to involuntary movements.

Adult onset Huntington's disease - Adult onset Huntington's disease is the most common form of the disease. The symptoms of this form of the disease usually develop in one's mid 30s and 40s.

Early onset Huntington's disease - Early onset Huntington's disease can begin in childhood. The symptoms of this form of the disease may look similar to Parkinson's disease like stiffness, tremors and slow movements.[8]

SYMPTOMS

Motor symptoms include a mixture of additional involuntary movements and impaired voluntary movements. These symptoms usually begin in the extremities of the body; like involuntary twitches in fingers, toes, and face. In the early years of HD a subtle loss of coordination, and trouble performing complicated motions also occurred. The most common motor symptom is chorea but severity varies greatly.[9,10]

Cognitive symptoms also become noticeable in the early stages of HD, as it becomes more difficult for people to think through complicated tasks. These cognitive changes can have a major impact on the patient. People can also become impulsive and this can result in reckless behavior.

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ISSN: 2347-7881

Psychiatric symptoms include depression and anxiety, apathy, irritability and aggression, psychosis and obsessive compulsive disorders. There is an increased risk of suicide.[9,11,12] All symptoms are described under following table No.1.

TABLE 1 Showing symptoms related to HD

COMMON CLINICAL SIGNS AND SYMPTOMS[12]			
Motor	**Cognitive**	**Psychiatric**	**Other**
Chorea	Increasing difficulties with:	Depression	Weight loss
Impaired gait	Planning	Anxiety	Sleep disturbances
Impaired postural reflexes	Organization	Irritability	Incontinence (usually later in disease)
Dysphagia	Multitasking	Aggression	
Dysarthria and dysphasia	Judgment	Apathy	
Balance and co-ordination problems	Impulse control	Obsessive compulsive disorder	
Rigidity, dystonia and bradykinesia	Inflexible thinking	Suicide	
Eye movement abnormalities	Concentration	Disorders of sexual function	
	Memory	Psychosis	
	Insight		
	Denial		
	Perseveration		

PATHOPHYSIOLOGY OF HUNTINGTON DISEASE

The various discoveries proven that HD gene mutation and the repeat expansion play an important role in the pathophysiology of the disease. The genetic defect underlying Huntington's disease is an unstable, caused by an abnormal CAG expansion within the first exon of the Huntingtin gene (HTT), leading to an expanded polyglutamine (polyQ) track in the HTT protein. Disease-causing mutations have a CAG repeat length of 40 or more.[13] HTT Huntingtin is a 348-kDa protein that is ubiquitously expressed with highest levels found in neurons. It is primarily cytoplasmic, but it also localizes to the nucleus and organelles, with higher expression levels in brain and testis. The polyQ expansion in the HTT protein leads to protein aggregation and cell toxicity. The mechanisms by which the mutant HTT protein induces a cascade of cellular changes, leading to cell dysfunction and degeneration, have not yet been fully elucidated. Modulation of genetic functioning through the IT15 gene, neuronal death in relation to intranuclear inclusions of aggregated mutant Htt, and progressive cerebral degeneration starting in the caudate nucleus and the putamen may all be part of the pathophysiology of Huntington's disease (Figure 1).[14,15,16,17]

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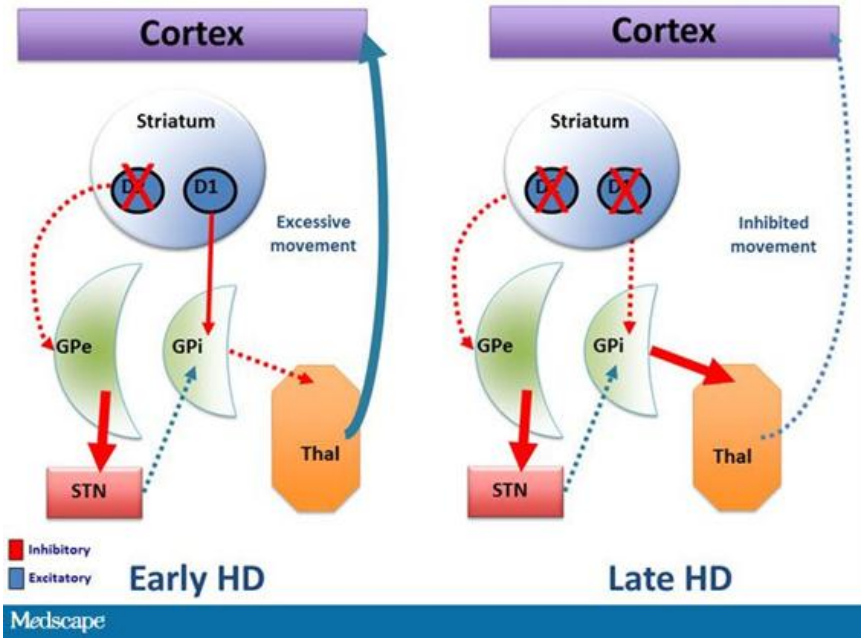

Figure 1

Mutant huntingtin adversely affects a congregation of intracellular processes and causes widespread interruption consists of:

- Mitochondrial dysfunction
- Disrupted calcium signaling
- Alterations in proteosomal function
- Transcriptional dysregulation of various genes
- Autophagy
- Altered axonal transport of critical factors
- Abnormal protein interactions

In addition to the widely described pathogenic role of expanded polyQ tracks, several studies have also shown that different neurodegenerative disorders caused by trinucleotide repeat expansions may involve RNA-mediated mechanisms. These include the sequestration of RNA-binding proteins by the expanded trinucleotide repeats, and activation of a variety of pathways such as RNA interference (RNAi) and protein misfolding pathways. The understanding of how expanded-repeat RNAs confer neurotoxicity is crucial to developing effective treatments.[18,19]

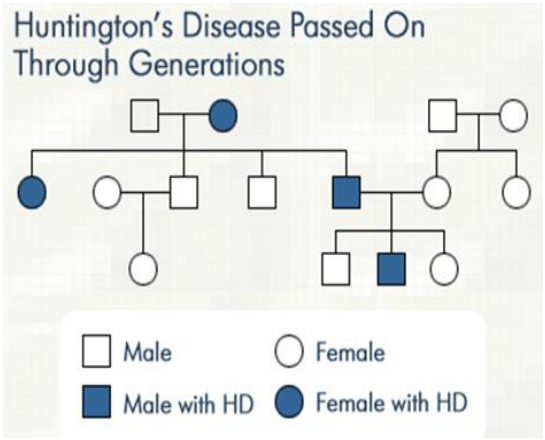

Figure 2

TREATMENT

Current Pharmacological Treatment

There is no cure for Huntington disease. There is no known way to stop the disease from getting worse. The duration between onset and severe disability or death averages 17 years. The goal of treatment is reduction of movement disorders and psychiatric symptoms. Therapeutic intervention has been restricted to genetic counseling (pre- and post-diagnosis), symptom management and palliative care.[20] Figure shows therapeutic targets for HD.

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ISSN: 2347-7881

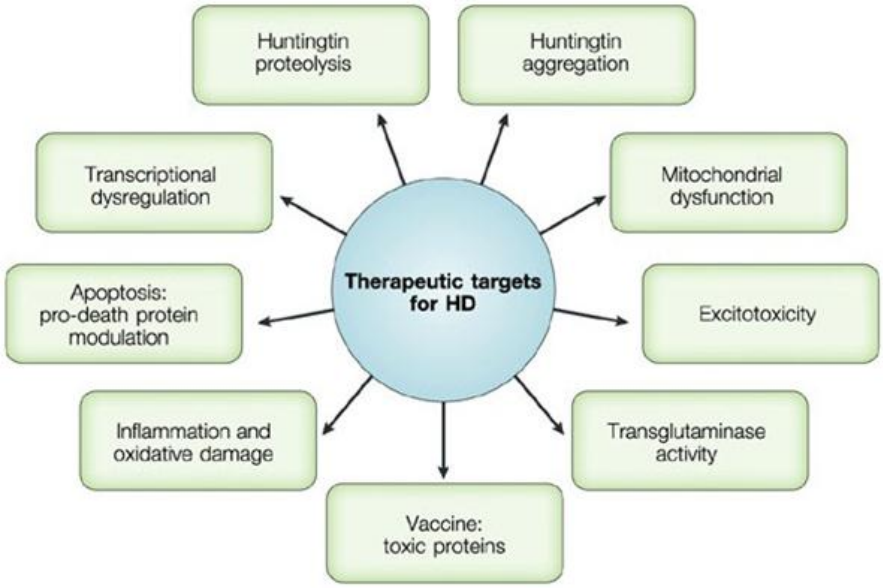

Figure 3

Tetrabenazine is efficient in the management of HD and has been shown to reduce chorea. Tetrabenazine works mainly as a vesicular monoamine transporter (VMAT) inhibitor, therefore promoting the early metabolic degradation of monoamines, especially the neurotransmitter dopamine. In the central nervous system, VMAT is the only transporter that transports cytoplasmic dopamine into synaptic vesicles for storage and subsequent exocytotic release.[21]Apart from this It is also important to assess patients for depression, psychosis and suicidal thoughts so as to prescribe following drugs if necessary.

Antipsychotics(hallucinations, delusions, violent outbursts): haloperidol, chlorpromazine, olanzapine (contraindicated if patient has dystonia)

Antidepressants (depression, obsessive-compulsive behavior): fluoxetine, sertraline hydrochloride, nortriptyline

Tranquilizers (anxiety, chorea): benzodiazepines, paroxetine, venlafaxin, beta-blockers

Mood-stabilizers (mania, bipolar disorder): lithium, valproate, carbamazepine

Botulinum toxin (dystonia, jaw clenching).[22,23]

Therapeutic advances

Therapeutic advances unleashed another fact that HD patients has also shown a significant reduction in the enzymes producing gamma-aminobutyric acid (GABA) and acetylcholine (Ach) in the striatum, indicating the extensive loss of GABA-ergic and cholinergic striatal neurons. Although most therapeutic advances in publication have only been tested on animal models, they offer insight into possible treatment of HD in the near future.[24]

Stem cell Therapy

Various pre-clinical studies have utilized stem or progenitor cells for transplantation therapy using HD animal models. In several studies, neural stem and progenitor cells used as allotransplants and xenografts have been shown to be capable of surviving transplantation and differentiating into mature GABAergic neurons, resulting in behavioral improvements. These studies have proven the potential of stem cells for transplantation therapy in HD. It also becomes clear that technical and ethical issues regarding the

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ISSN: 2347-7881

availability of stem cells must be solved before human trials can be conducted.[25]

A number of behavioral treatment strategies have been proposed to reduce some of the more disabling aspects of certain symptoms associated with Huntington's disease. Early intervention with speech therapy to provide alternative communication strategies may also be of benefit. Relaxation therapies and cognitive behavior therapies may be of value in the treatment of affective disturbances. Family counseling may provide an invaluable therapeutic outlet for the distress that family members will have to endure throughout there lative's illness.[26]

CONCLUSION

The present epoch is one of marvelous enthusiasm and rapid revolution in Huntington's disease (HD) research. Discovery of the gene and the subsequent development of transgenic mouse models of HD have been major breakthroughs. However, the etiology of the disease and its pathogenesis continue to be poorly understood and current treatment approaches have remained relatively primitive. Some hope for the future has been offered by a number of recent developments in Huntington's disease research. The main challenge in finding a cure for HD is the selection of molecular targets. Although clinical trials have yet to support a safe and effective therapeutic agent, an increased understanding of the pathophysiology and molecular biology of the disorder may well offer new treatment avenues. Recent applications of cell transplantation technology to Huntington's disease may also provide some hope for the future. Although much remains to be done, this project report provides us with an update on the most salient advances made in the past decade in the field of HD, suggests pathological scenarios as to how mutant huntingtin may lead to HD, and most importantly, discusses the many steps in the process of functional decline and cell death that might be targeted by new neuroprotective therapies.

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