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RESEARCH ARTICLE

A COMPREHENSIVE REVIEW ON HUNTINGTON'S DISEASE

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ABSTRACT

Huntington's disease (HD) is an incurable, inherited, progressive, neurodegenerative disorder that is characterized by a triad of the motor, cognitive, and psychiatric problems. Despite the noticeable increase in therapeutic trials in HD in the last 20 years, there have, to date, been very few significant advances. Prevalence in the Western populations is estimated at 10.6 to 13.7 individuals per 1 lakh. The mean age at onset of symptoms is 30 to 50 years. In some cases, symptoms start before the age of 20 years with behavior disturbances and learning difficulties at school. Diagnosis is based on clinical symptoms and signs in an individual with a parent with proven HD and is confirmed by DNA determination. Pre-manifest diagnosis should only be performed by multidisciplinary teams in healthy at-risk adult individuals who want to know whether they carry the mutation or not. Until now an actual remedy for the HD is not available. Management should be multidisciplinary and is based on treating symptoms to improve quality of life. In this review, we discuss the status of and supporting evidence for, potential novel treatments of HD.

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INTRODUCTION

In 1872 George Huntington wrote an account of hereditary chorea, which is now known as HDis an inherited disorder that results in the death of brain cells (Yu *et al.*,2017).He described its hereditary nature, associated psychiatric and cognitive symptomsand the manifestation of the disease in adult life between 30 and 40 years of age (Ghosh & Tabrizi, 2018). He outlined the progressive nature of the disease stating, 'Once it begins it clings to the bitter end'. However, the monogenic nature and full penetrance of HD makes it perhaps one of the most treatable neurodegenerative diseases (Van Duijn, 2017).This has become particularly apparent inthe last decade with the advent of new therapeutic approaches that can directly target the HD gene and prevent the production of the toxic mutant hunting tin(HTT)protein (Baake& Dumas, 2017).

ETIOLOGY

HD is caused by an autosomal dominantly inherited cytosine-adenine-guanine (CAG)trinucleotide repeatexpansionin the HTT gene on chromosome number-4 (Rodrigues *et al.,* 2017).

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This results in the production of mutant HTT protein with an abnormally long polyglutamine repeat. Those with greater than 39 CA Grepeats are certain to develop the disease, whilst reduced penetrance is seen between 36 and 39 repeats (Silva *et al.,* 2017).Anticipation can be seen when the gene is passed down the paternal line, such that a father with a CAG repeat length in the intermediate range may have a child with an expanded pathogenic repeat length (Kay &Collins, 2018). This is because sperm from males shows greater repeat variability and larger repeat sizes than somatic tissues (Figure 1) (Watersa *et al.,* 2018). This change results in a larger form of HTT. This is toxic, and, as it accumulates in the brain, it causes damage to brain cells. Some brain cells are sensitive to the larger form of HTT, especially those related to movement, thinking, and memory (Cubo *et al.,* 2016). It undermines their function and eventually destroys them. Scientists are not sure exactly how this happens (Sun *et al.,* 2017).

EPIDEMIOLOGY

The worldwide prevalence of HD is 5 to 10 cases per 1 lakh personsbut varies greatly geographically as a result of ethnicity, local migration, and past immigration patterns. Prevalence is similar for men and women. The rate of occurrence is higher in peoples of Western European descent, averaging around 7 per 1 lakh people, and is lower in the rest of the world; e.g., one per million people of Asian and African descent (Keum *et al.*, 2016).

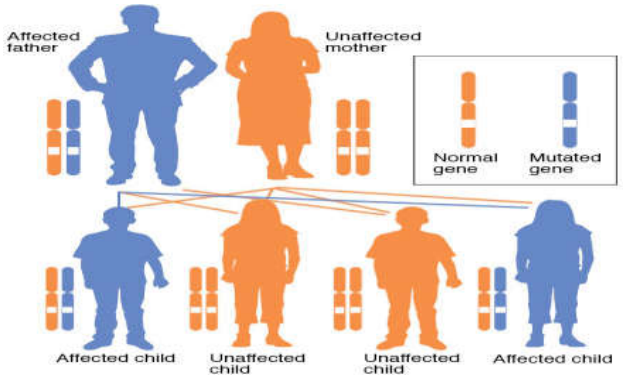

Figure 1. Autosomal dominant inheritance pattern.

A 2013 epidemiological study of the prevalence of HD in the United Kingdom (UK) between 1990 and 2010 found that the average prevalence in the UK was 12.3 per 1 lakh. Additionally, some localized areas have a much higher prevalence than their regional average (Hensman Moss *et al.,* 2017). One of the highest incidences is in the isolated populations of the Lake Maracaibo region of Venezuela, where HD affects up to 700 per 1 lakh persons. Other areas of high localization have been found in Tasmania and specific regions of Scotland, Wales, and Sweden (Das *et al.,* 2016). Increased prevalence in some cases occurs due to a local founder effect, a historical migration of carriers into an area of geographic isolation.Some of these carriers have been traced back hundreds of years using genealogical studies. Genetic haplotypes can also give clues for the geographic variations of prevalence (C Yuen *et al.,* 2017). Iceland, on the contrary, has a rather low prevalence of 1 per 1 lakh, although Icelanders as a people are descended of the early Germanic tribes of Scandinavia which also gave rise to the Swedes (Dolzhenko *et al.,* 2017); all cases except for one going back nearly two centuries having derived from the offspring of a couple living early in the 19th century. Finland, as well, has a low incidence of only 2.2 per 1 lakh people (Mason & Barker, 2016).

PATHOGENESIS

HD is genetically inherited in an autosomal dominant fashion with a prevalence of about 1 in 75hundred individuals in the general population. The normal allele has less than 27 CAG repeats and intermediate alleles have 27 to 35 repeats (Pollock & Dahlenburg, 2016). CAG repeats of 36 to 39 will develop HD with less penetrance. Individuals who have40 or more CAG repeats will develop HD with full penetrance (Galeano *et al.,* 2018). It is also reported that the higher the CAG expansion, the earlier the onset and the greater the disease severity. Reported the largest expansion of 121 trinucleotides (Salama *et al.,* 2017).CAG codon encodes glutamine-amino acid. Glutamine is synthesized from glutamate and ammonia by the enzyme glutamine synthetase. It is mainly produced in muscle, the lungs, and the brain and acts as aprecursor to the neurotransmitter glutamate (Yang *et al.*, 2017). CAG has glutamine amino acids within the HTT gene and it is not toxic in itself (Alpaugh *et al.,* 2017). However, the polyglutamine expansion involves the formation of aggregate and ultimately becomes toxic. It is the principal factor for the manifestation of HD because aggregates are never a remarkable feature in the brain of normal subjects (Naaldijk *et al.,* 2017). Aggregate formations are accountable for secondary problems, like inflammatory responses (altered cytokine and nitric oxide level), mitochondrial dysfunction (imbalanced level of free radicals and oxidative stress markers),nuclear cleavage, apoptosis, excitotoxicity, transcriptional altered regulation, and lastly, are responsible for the altered neuropath logical feature (cause of cell death/damage) (Figure 2) (Ellrichmann *et al.,* 2017). Approximately 70%of the variation of the disease is due to expanded CAG repeats, while 13% of the variation is due to polymorphisms in the glutamate ionotropic receptor kainate type subunit-2 gene (Kumar *et al.*, 2017).

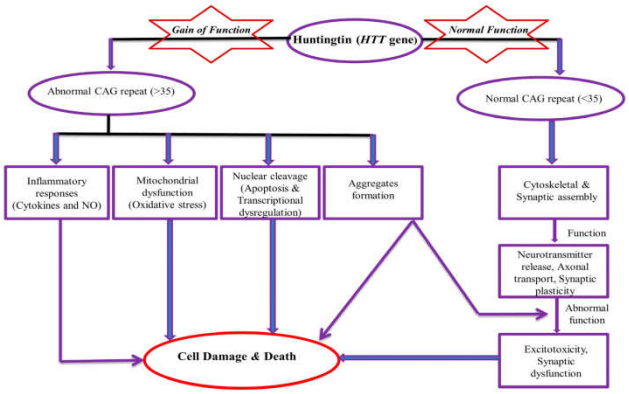

Figure 2: Mechanism of toxicity of the HTT gene.

Clinical symptoms: According to the Huntington's Disease Society of America, the key symptoms include personality changes, mood swings, and depression problems with memory and judgment unsteady walk and uncontrollable movements difficulty speaking and swallowing, and weight loss (Table 1) (Thomi *et al.,* 2019). In some people, depression occurs before motor skills are affected. Mood swings and unusual behavior are common early signs (Buijsen *et al.,* 2019).

Table 1:During the HD, disorders affecting the functional ability of patients

Disorders	Descriptions
Movement disorders	The movement disorders associated with HD can include both involuntary movement problems and impairments involuntary movements, such as involuntary jerking or writhing movements (chorea), muscle problems, such as rigidity or muscle contracture (dystonia).
Cognitive disorders	Cognitive impairments often associated with HD include difficulty organizing, prioritizing or focusing on tasks; Lack of flexibility or the tendency to get stuck on a thought, behavior or action (perseveration); Lack of impulse control that can result in outbursts, acting without thinking and sexual promiscuity; Lack of awareness of one's behaviors and abilities; Slowness in processing thoughts or "finding" words; Difficulty in learning new information.
Psychiatric disorders	The most common psychiatric disorder associated with HD is depression. This is not simply a reaction to receiving a diagnosis of HD. Instead, depression appears to occur because of injury to the brain and subsequent changes in brain function. Other common psychiatric disorders include (a) **Obsessive-compulsive disorder: A** condition marked by recurrent, intrusive thoughts and repetitive behaviors. (b) **Mania:** Which can cause elevated mood, overactivity, impulsive behavior 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 HD, especially as the disease progresses.

Table 2:Some diagnostic tests for confirmed to HD

Tests	Descriptions
Neurological tests	Tests of neurological and physical functions may review reflexes, balance, movement, muscle tone, hearing, walking, and mental status. Some laboratory tests may be ordered as well, and individuals with HD may be referred to other health care professionals such as psychiatrists, genetic counselors, clinical neuropsychologists, or speech pathologists for specialized management and/or diagnostic clarification. A tool used by physicians to diagnose HD is to take the family history, sometimes called a pedigree or genealogy.
Genetic tests	The most effective and accurate method of testing for HD called the direct genetic test-counts the number of CAG repeats in the HD gene, using DNA taken from a blood sample. The presence of 36 or more repeats supports a diagnosis of HD. A test result of 26 or fewer repeats rules out HD. A small percentage of individuals will have repeats in a borderline range. For such individuals, physicians may try to get a clearer picture of disease risk by asking other family members to come in for the examination and genetic testing. Before the availability of the direct genetic test, clinics used a method called linkage testing. A version of the linkage method is sometimes still used for prenatal testing (Southwell *et al.*, 2017).
Diagnostic imaging	In some cases, especially if a person's family history and genetic testing are inconclusive, the physician may recommend brain imaging, such as computed tomography (CT) or, more likely, magnetic resonance imaging (MRI). As the disease progresses, these scans typically reveal shrinkage of the striatum and parts of the cortex, and enlargement of fluid-filled cavities within the brain called ventricles. These changes do not necessarily indicate HD, however, because they can occur in other disorders. Conversely, a person can have early symptoms of HD and still have normal findings on a structural CT or MRI scan (Miniarikova *et al.*, 2017).
Prenatal testing	Prenatal diagnosis is the process of testing a fetus while in the pregnant uterus to determine if the fetus has inherited HD or not. This can be done in two different ways: (a) Chorionic Villus Sampling (CVS) is done typically between 10 to 13 weeks of pregnancy. A piece of the developing placenta is removed either through a woman's cervix or abdomen using a catheter or needle. This tissue is 99% genetically identical to the fetus, so DNA testing can be done for HD status and a result given. CVS carries a risk of miscarriage that can vary slightly from center to center but is usually in the range of 1 per 100 to 1 per 500. (b) Amniocentesis is typically performed between 15 to 20 weeks of pregnancy. The amniotic fluid that surrounds the fetus is removed from the uterus using a thin needle. This fluid contains cells from the fetus that can be isolated, grown in the laboratory, and tested for HD status. Again, amniocentesis carries a risk of miscarriage that can vary slightly from center to center but is usually in the range of 1 per 200 to 1 per 500 (Evers *etal.*, 2018).

Table 3:Drugs to treat movement disorders

Drug therapy	Descriptions
Tetrabenazine	It is specifically approved by the Food and Drug Administration to suppress the involuntary jerking and writhing movements associated with HD. A serious side effect is a risk of worsening or triggering depression or other psychiatric conditions (Ferrari Bardile *et al.*, 2019).
Haloperidol and chlorpromazine	They have a side effect of suppressing movements. Therefore, they may be beneficial in treating HD. However, these drugs may worsen involuntary contractions and muscle rigidity (Sehara *et al.*, 2017).
Amantadine, levetiracetam, and clonazepam	Other medications that may help suppress HD include amantadine, levetiracetam and clonazepam At a high dose of amantadine can worsen the cognitive effects of HD. It may also cause leg swelling and skin discoloration and also have a high risk of drug dependence and abuse (Andrews *et al.*, 2018).

(b) Drug therapy for psychiatric disorders:

Table 4:Possible drugs to treat psychiatric disorders and related symptoms

Drug therapy	Descriptions
Citalopram, escitalopram, fluoxetine, and sertraline	These drugs may also have some effect on treating obsessive-compulsive disorder. Side effects may include nausea, diarrhea, drowsiness and low blood pressure (Kang*et al.*, 2019).
Quetiapine, risperidone, and olanzapine	These drugs may suppress violent outbursts, agitation, and other symptoms of mood disorders or psychosis. However, these drugs may cause different movement disorders (Gardinerb *et al.*, 2019).
Valproate, carbamazepine, and lamotrigine	**Mood-stabilizing drugs** that can help prevent the highs and lows associated with bipolar disorder include anticonvulsant drugs (De Rycke *et al*., 2017).

Diagnosis: A diagnosis of HD is generally based on findings from neurological, psychological, genetic testing, and prenatal testing (Table 2) (Tabrizi *et al.,* 2019).

Treatment: There's currently no cure for HD or any way to stop it from getting worse. Manydrugs may be prescribed to help control emotional and movement problems associated with HD (Table 3) (Spronck *et al.,* 2019). Most of the drugs available for HD symptoms work by modulating neurotransmitters-the chemical messages that shuttle between neurons (Table 4) (Samaranch *et al.,* 2017). For many of these drugs, their mechanisms of action against HD are not fully understood.Research into new treatments is ongoing and there have been some promising results recently.

Conclusion

HDis a progressive and devastating disease. Although major advances have been made in the clinical, genetic, and neuropath logical understanding after the discovery of the mutation that causes HD, therapeutic options are still limited to symptomatic medication and supportive approaches. To date few treatments are available and many clinical trials have failed. In the future treatments might be initiated in the premani fest phase, with the hope of delaying or halting the disease process itself.

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