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HUNTINGTON'S DISEASE: FROM MOLECULAR PATHOGENESIS TO CLINICAL TREATMENT

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ABSTRACT

Huntington disease (HD) is a rare neurodegenerative disorder of the central nervous system characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia. Prevalence in the Caucasian population is estimated at 1/10,000-1/20,000. Mean age at onset of symptoms is 30-50 years. In some cases symptoms start before the age of 20 years with behavior disturbances and learning difficulties at school. HD is an autosomal dominant inherited disease caused by an elongated CAG repeat (36 repeats or more) on the short arm of chromosome 4p16.3 in the Huntingtine gene. Diagnosis is based on clinical symptoms and signs in an individual with a parent with proven HD, and is confirmed by DNA determination. There is no cure. Management should be multidisciplinary and is based on treating symptoms with a view to improving quality of life. The progression of the disease leads to a complete dependency in daily life, which results in patients requiring full-time care, and finally death. Thus, Huntington's disease is also emerging as a model for strategies to develop therapeutic interventions, not only to slow progression of manifest disease but also to delay, or ideally prevent, its onset.

Keywords: Huntington disease, Neurodegenerative, Dementia, Autosomal dominant, Huntingtine gene, Psychiatric disturbances.

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. It is a neurodegenerative disorder passing within families from generation to generation with onset in middle age and characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia[1] 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 (HD). In 1983, a linkage on chromosome 4 was established and in 1993 the gene for HD was found.[2] That period marked a tremendous increase in interest in HD and neurogenetic disorders. For the first time, actual premanifest diagnoses could be made and as more diseases involving trinucleotide repeats of CAG were found, HD served as a model for many studies in medicine. CAG (cytosine (C), adenine (A), and guanine (G)), is a trinucleotide, the building stone of DNA. CAG is the codon for the amino acid glutamine. Finding the gene opened new research lines, new models and for the first time a real rationale on the way to treat this devastating disease. Many symptomatic treatments are now available, but there is a need for better, modifying drugs.

Historical Background

HD is also known as Huntington's chorea. Although an epidemic of dancing mania was described in 1374, it was Paracelsus (1493–1541)

who first used the term *chorea* to define this movement disorder, suggesting its central nervous system (CNS) origin.[3] In the following years, until the 17th century, the disease had remained obscure and its nature had not been understood. In 1600, English colonists used the name "that disorder" or "San Vitus" dance to refer to HD. In those days, people with chorea, because of the involuntary muscle jerks and twitches characteristic of HD, were often thought to be possessed by the devil. It is believed that at least one of the alleged witches executed in Salem (Massachusetts) in the 1690s had HD. A first attempt of a medical description for HD as "chronic hereditary chorea" was made two centuries later, in the 1840s, by physicians in the United States, England, and Norway. However, the first accurate description of the disease came about 30 years later, in 1872, by a 22-yr-old American doctor, George Huntington, working in Long Island, New York, who wrote a brief, uniform, anecdotal, and entirely unreferenced paper called *On Chorea* published in the Medical and Surgical Reporter of Philadelphia (Volume 26, No. 15, April 13, 1872).[4] The genetic nature of the disease led to more than a century of attempts to identify those large communities of persons at risk to develop HD. In the early 1920s, the American eugenicist Charles B. Davenport tracked families with inherited disorders, producing what was, at the time, the largest study of families with HD. Later, in the 1950s, Dr. Amerigo Negrette diagnosed HD in a large community of people living around Lake Maracaibo, Venezuela, which 20 years later became the center of a breath-taking crusade towards the discovery of the HD gene,[5] made possible thanks to the remarkable efforts of Nancy Wexler, a neuropsychologist at Columbia University and cofounder of the Hereditary Disease Foundation (HDF), and of the many scientists and clinicians from the Boston area and other parts of the world.

What Is Huntington Disease?

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin.[6] A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition.[7] Juvenile Huntington disease tends to progress more quickly than the adult-onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.

Anticipation

Anticipation, the phenomenon in which increasing disease severity or decreasing age of onset is observed in successive generations, is known to occur in HD. Anticipation occurs more commonly in paternal transmission of the mutated allele. The phenomenon of anticipation arises from instability of the CAG repeat during spermatogenesis. Large expansions (i.e., an increase in allele size of >7 CAG repeats) occur almost exclusively through paternal transmission. Most often children with juvenile-onset disease inherit the expanded allele from their fathers, although on occasion they inherit it from their mothers.[8]

Nomenclature

In the premolecular genetic era there were many different names for chorea, including St. Vitus

Dance and Sydenham's chorea. Juvenile HD, or childhood-onset HD, was previously called the Westphal variant of HD. Individuals who do not yet show symptoms are in the premanifest phase of HD.[9] Individuals who have been diagnosed with chorea and/or other validated signs of HD have manifest HD.

How Common Is Huntington Disease?

The prevalence of Huntington disease (HD) is between three and seven per 100,000 in populations of western European descent. HD appears less frequently in Japan, China, and Finland, and among African blacks. The frequency of HD in Japan has been estimated at between 0.1 and 0.38 per 100,000. The prevalence of HD exceeds 15 per 100,000 in some populations, mostly of western European origin.[10] The identity of the genetic change responsible for HD was first described in individuals living in the Lake Maracaibo region of Venezuela, which is believed to have the highest prevalence of HD in the world.[11] The uneven distribution of HD is at least partially explained by the distribution of specific predisposing alleles and haplotypes in the normal population of these ethnic groups.[11] It is not clear whether this predisposition for CAG expansion of specific haplotypes is simply the result of increases in background CAG size, or whether these haplotypes contain *cis* elements conferring a predisposition to instability.

ASSESSMENTS

The clinical assessment of the symptoms and signs of HD is important for patient, family and care-givers. To follow the patient systematically, mainly for research purposes, several scales have been developed. The best known are the Shoulson and Fahn capability scale[12] and the Unified Huntington Disease Rating Scale (UHDRS).[13,14] The UHDRS consists of a motor, behaviour, cognitive and functional part, preceded by a history and medication scheme. For the behaviour signs a new scale was developed by Craufurd: the Problem Behaviour Scale (PBS).[15] Other scales, for instance for the quality of life, are also in use. In the European Network for Huntington disease, a whole set of assessment scales has been devised,

which are now in use for over 6,000 patients in Europe.

What Genes Are Related To Huntington Disease?

Mutations in the *HTT* gene cause Huntington disease. The *HTT* gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain. The *HTT* mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times.[16] People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

Genetic Modifiers of HD

Although there is a correlation between CAG repeats length and age at onset of motor symptoms, HD patients may differ dramatically in age of onset and disease manifestations, despite similar CAG repeat lengths. Several studies revealed that a large set of genes distinct from the HD locus itself could contribute to modify disease onset and progression.[17] Early studies showed that genetic polymorphisms adjacent to the CAG repeats could influence the disease onset.[18,19] To date, several genetic modifiers of HD have been described. All of these modifiers relate to various mechanisms implicated in HD pathology as excitotoxicity, dopamine toxicity, metabolic

impairment, transcriptional deregulation, protein misfolding, and oxidative stress. Genetic analyses showed that patients carrying the Δ2642 glutamic acid polymorphism (a deletion of three nucleotides encoding for glutamic acid at codon position 2642–2645) develop the disease earlier than predicted by their CAG number in the HD gene.[20,21] Subsequent studies revealed that polymorphisms in genes encoding for the kainate-specific glutamate receptor GluR6, the apolipoprotein E ε2ε3 genotype, the polymorphic (Gln-Ala)$_{38}$ repeat in the transcriptional coactivator CA150, the *N*-methyl-D-aspartic acid (NMDA) receptor subunit 2B (GRIN2B), the ubiquitin COOH-terminal hydrolase L1 (UCHL1)[22], TP53 and hCAD, apoptosis signal-regulating kinase 1 (ASK1), mitogen-activated protein kinase kinase 6 (MAP2K6), and PPAR-γ coactivator 1α (PGC-1α) may be modifiers of age of onset in HD.

Modeling HD

Beyond what is currently feasible methodologically when using post mortem human brain samples, research on HD largely depends on animal (and cellular) models. In this section we offer an overview of the wide range of HD animal models available to the HD community. These models have been successfully used to investigate pathological pathways, molecular targets, and therapeutics.

Chemical Models

Before the identification of the disease gene, HD animal models were produced by injecting neurotoxins into the striatum. The initial reports demonstrating that direct intrastriatal injection of kainate, a non-NMDA glutamate agonist, could mimic in rats the axon-sparing striatal lesion observed in the human HD, represented the starting point of a wide literature on the use of glutamate analogs to produce striatal selective neurodegeneration in rodents.[23] Quinolinic acid and kainic acid have been the two most commonly used agents to produce rodent and non-human primate models of HD, suggesting that excitotoxicity could participate in the cell death observed in the disease.[24,25] Later studies indicated

that injection of mitochondrial toxins such as 3-nitropropionic acid and malonic acid were capable of replicating some of the behavioral aspects of HD in rats, indicating that mitochondrial dysfunction may also participate in HD pathogenesis.[26]

Genetic Models

It is now possible to monitor the actions of either normal or mutant huntingtin at tissue and subcellular levels at different time points.

In particular, HD cell lines, which allow the stable or inducible expression of wild-type or mutant huntingtin, have been useful for the dissection of disease mechanisms, and they have been recently exploited for the screening of therapeutics.[27,28] The actual effort is towards the production of novel in vitro cellular systems based on the propagation and differentiation of neural stem cells bearing the mutant gene that can be used for drug discovery and toxicology tests in short-term applications. More recently, the induced-Pluripotent Stem (iPS) technology was used for the pathological modeling of Spinal Muscular Atrophy (SMA), and efforts are currently underway to derive iPS cells from HD patients.

How Do People Inherit Huntington Disease?

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington disease does not have a parent with the disorder. As the altered *HTT* gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats is usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. People with the adult-onset form of Huntington disease typically have 40 to 50 CAG repeats in the *HTT* gene,[29] while people with the juvenile form of the disorder tend to have more than 60 CAG repeats. Individuals who have 27 to 35 CAG repeats in the *HTT* gene do not develop Huntington disease, but they are at risk of having children who will develop the disorder. As the

gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington disease (36 repeats or more).

Symptoms

Huntington's disease usually causes movement, 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 movements and impairments in voluntary movements:

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

Impairments in voluntary movements-rather than the involuntary movements-may have a greater impact on a person's ability to work, perform daily activities, communicate and remain independent.[31]

Cognitive Disorders

Cognitive impairments often associated with Huntington's disease 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 own behaviors and abilities
- Slowness in processing thoughts or "finding" words
- Difficulty in learning new information

Psychiatric Disorders

The most common psychiatric disorder associated with Huntington's disease is depression. This isn't simply a reaction to receiving a diagnosis of Huntington's disease. Instead, depression appears to occur because of injury to the brain and subsequent changes in brain function. Signs and symptoms may include:

- Feelings of irritability, sadness or apathy[32]
- Social withdrawal
- Insomnia
- Fatigue and loss of energy
- Frequent thoughts of death, dying or suicide

Other common psychiatric disorders include:

Obsessive-Compulsive Disorder

A condition marked by recurrent, intrusive thoughts and repetitive behaviors

Mania

This can cause elevated mood, overactivity, impulsive behavior and inflated self-esteem

Bipolar Disorder

Or 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.[33]

Secondary Symptoms and Signs

From early on, an unintended weight loss has been reported in all patients. As more attention is now paid to this phenomenon, the loss seems to be a little less severe, the cause being diverse. Although it seems logical to think that chorea should play the main role in weight loss, it has been shown that there is no relation between weight loss and chorea or other movement disorders. A relation with the length of the CAG repeat has been described [34]. More practical issues, such as slower functioning, decreased appetite, difficulty handling food and swallowing certainly play a role. But hypothalamic neuronal loss is also a causative factor.[35,36] Attention has only recently been focused on sleep- and circadian rhythm disturbances of patients with HD.[37] Autonomic disturbances can result in attacks of profuse sweating.

Depression and Suicide Risk

The incidence of depression in preclinical and symptomatic individuals is more than twice the general population.[38] The etiology of depression in HD is unclear; it may be a pathologic rather than a psychological consequence of having the disease.[39] Suicide and suicide ideation are common in persons with HD, but the incidence rate changes with disease course and predictive testing results.[40,41,42] The critical periods for suicide risk were found to be just prior to receiving a diagnosis and later, when affected individuals experience a loss of independence.[43,44]

Other

Persons with HD tend to have a lower body mass index than controls, which may be related to altered metabolism.[45] Individuals with HD also demonstrate disturbed cholesterol metabolism.[46] It is also common for persons with HD to demonstrate increased appetite and energy expenditure. Sleep and circadian rhythms are disrupted in individuals with HD, possibly as a result of hypothalamic dysfunction and/or alterations in melatonin secretion. Insomnia and daytime somnolence may also be present, although this is more commonly due to psychiatric changes, depression, or chorea.[47]

Symptoms of Juvenile Huntington's Disease

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

Behavioral Changes

- Loss of previously learned academic or physical skills
- Rapid, significant drop in overall school performance
- Behavioral problems[48]

Physical Changes

- Contracted and rigid muscles that affect gait (especially in young children)
- Changes in fine motor skills that might be noticeable in skills such as handwriting

- Tremors or slight involuntary movements[48]
- 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 -one copy from each parent. A parent with a defective Huntington gene could pass along the defective copy of the gene or the healthy copy.[49] Each child in the family, therefore, has a 50 percent chance of inheriting the gene that causes the genetic disorder.

Complications

After the onset of Huntington's disease, a person's functional abilities gradually worsen over time. The rate of disease progression and duration varies. The time from disease onset to death is often about 10 to 30 years. Juvenile onset usually results in death within 10 years. The clinical depression associated with Huntington's disease may increase the risk of suicide. Some research suggests that the greater risk of suicide occurs before a diagnosis is made and in middle stages of the disease when a person has begun to lose independence.[50]

Eventually, a person with Huntington's disease requires help with all activities of daily living and care. Late in the disease, he or she will likely be confined to a bed and unable to speak. However, he or she is generally able to understand language and has an awareness of family and friends.

Common causes of death include:

- Pneumonia or other infections
- Injuries related to falls
- Complications related to the inability to swallow

Tests and Diagnosis

A diagnosis of Huntington's disease is based primarily on patients' answers to questions, a general physical exam, a review of your family medical history, and neurological and psychiatric examinations.

Neurological Examination

The neurologist will ask some questions and conduct relatively simple tests in the office to judge:[51]

Motor Symptoms

- Reflexes
- Muscle strength
- Muscle tone
- Coordination
- Balance

Sensory Symptoms

- Sense of touch
- Vision and eye movement
- Hearing

Psychiatric Symptoms

- Mental status
- Mood

Neuropsychological Testing

The neurologist may also perform standardized tests to assess:[52]

- Memory
- Reasoning
- Mental agility
- Language function
- Spatial reasoning

Psychiatric Evaluation

Patients will likely be referred to a psychiatrist for an examination to judge a number of factors that could contribute to their diagnosis, including:

- Emotional state
- Patterns of behaviors
- Quality of judgment
- Coping skills
- Signs of disordered thinking[53]
- Evidence of substance abuse

Brain Imaging and Function

Doctor may order brain-imaging tests for assessing the structure or function of the brain. The imaging technologies may include MRI, which can produce detailed cross-sectional and 3-D images of the brain, or CT scan, which produces cross-sectional images.[54] These images may reveal structural changes at particular sites in the brain affected by Huntington's disease, although these changes may not be apparent early in the course of the disease. These tests can also be used to rule out other conditions that may be causing symptoms.

Genetic Counseling and Testing

If symptoms strongly suggest a diagnosis of Huntington's disease, the doctor may recommend a genetic test for the defective gene. This test can confirm the diagnosis, and it may be valuable if there's no known family history of Huntington's disease or if no other family member's diagnosis was confirmed with a genetic test. The test won't provide information that is beneficial in determining a treatment plan. Before undergoing such a test, the genetic counselor will explain the benefits and drawbacks of learning test results.[55] The genetic counselor can also answer questions about the inheritance patterns of Huntington's disease.

Predictive Genetic Test

A genetic test can be given to someone who has a family history of the disease but shows no signs or symptoms. This is called predictive testing. The test result has no treatment benefit, and it doesn't indicate when disease onset will begin or what symptoms are likely to appear first. Some people may elect to do the test because they find it more stressful not knowing. Others may want to take the test before they make decisions about having children. Risks may include problems with insurability or future employment and the stresses of facing a fatal disease.[56] These tests are only performed after consultation with a genetic counselor.

Prenatal Diagnosis

As the test can be performed on any cell with a nucleus containing DNA, antenatal diagnosis is also possible. Between the 10th and 12th weeks of pregnancy, chorionic villus sampling and between the 15th and 17th weeks amniocentesis can be performed and DNA-testing carried out. The procedure is only initiated if the parents already know their own genetic status to prevent unwanted disclosure for two individuals at the same time. The procedure is embarked on with the intention of ending the pregnancy if the HD gene is found in the embryo. The mother cannot be forced to agree

with this conclusion. If the parents have not yet been genotyped, one can opt for an exclusion test by comparing the genetic status of the embryo with that of the grandparents.[57] In this situation the result is either 0% risk for the foetus, and so the parent keeps his or her 50% status, or 50% risk for the foetus. The foetus has received a chromosome from the affected grandparent, but it is not known to which chromosome the HD gen is coupled. In this case the foetus has a 50% risk, comparable to the parent, and the parents can decide to abort a 50% at risk baby.

Treatments and Drugs

No treatments can alter the course of Huntington's disease. But medications can lessen some symptoms of movement and psychiatric disorders. And multiple interventions can help a person adapt to changes in his or her abilities for a certain amount of time. Medication management is likely to evolve over the course of the disease, depending on the overall treatment goals. Also, drugs to treat some symptoms may result in side effects that worsen other symptoms.[58]

Medications for Movement Disorders

Drugs to treat movement disorders include the following:

- *Tetrabenazine*
  Tetrabenazine (Xenazine) is specifically approved by the Food and Drug Administration 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 possible side effects include drowsiness, nausea and restlessness.

- *Antipsychotic drugs*
  Such as haloperidol (Haldol) and chlorpromazine, have a side effect of suppressing movements. Therefore, they may be beneficial in treating chorea. These drugs may, however, worsen involuntary contractions (dystonia) and muscle rigidity.[59]

Newer drugs, such as risperidone (Risperdal) and quetiapine (Seroquel), may have fewer side effects but still should be used with caution, as they may also worsen symptoms.

- *Other medications*
  That may help suppress chorea include amantadine, levetiracetam (Keppra) and clonazepam (Klonopin). 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 worsen the cognitive side effects of Huntington's disease and cause drowsiness. It also has a high risk of dependence and abuse.[60,61]

Medications for Psychiatric Disorders

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

- *Antidepressants*
  Include such drugs as citalopram (Celexa, Lexapro), fluoxetine (Prozac, Sarafem) and sertraline (Zoloft). These drugs may also have some effect on treating obsessive-compulsive disorder. Side effects may include nausea, diarrhea, drowsiness and low blood pressure.[62]

- *Antipsychotic drugs*
  Such as quetiapine (Seroquel), risperidone (Risperdal) and olanzapine (Zyprexa) — may suppress violent outbursts, agitation, and other symptoms of mood disorders or psychosis. However, these drugs may cause different movement disorders themselves.

- *Mood-stabilizing drugs*
  That can help prevent the highs and lows associated with bipolar disorder include anticonvulsants, such as valproate (Depacon), carbamazepine (Carbatrol, Epitol, Equetro) and lamotrigine (Lamictal). Common side effects include

weight gain, tremor and gastrointestinal problems.[63]

Psychotherapy

A psychotherapist -a psychiatrist, psychologist or clinical social worker-can provide talk therapy to help a person manage behavioral problems, develop coping strategies, manage expectations during progression of the disease and facilitate effective communication among family members.[64]

Speech Therapy

Huntington's disease can significantly impair control of muscles of the mouth and throat that are essential for speech, eating and swallowing. A speech therapist can help improve ability to speak clearly or teach to use communication devices-such as a board covered with pictures of everyday items and activities.[64] Speech therapists can also address difficulties with muscles used in eating and swallowing.

Physical Therapy

A physical therapist can teach appropriate and safe exercises that enhance strength, flexibility, balance and coordination. These exercises can help maintain mobility as long as possible and may reduce the risk of falls. Instruction on appropriate posture and the use of supports to improve posture may help lessen the severity of some movement problems. When the use of a walker or wheelchair is required,[65] the physical therapist can provide instruction on appropriate use of the device and posture. Also, exercise regimens can be adapted to suit the new level of mobility.

Occupational Therapy

An occupational therapist can assist the person with Huntington's disease, family members and caregivers on the use of assistive devices that improve functional abilities. These strategies may include:

- Handrails at home
- Assistive devices for activities such as bathing and dressing
- Eating and drinking utensils adapted for people with limited fine motor skills.66

Therapies under Investigation

A wide range of potential therapeutics are under investigation in both animal models of HD and human clinical trials.[67] This diversity reflects the variety of cellular pathways that are known to be perturbed in HD. Pharmacologic agents being investigated include inhibitors of apoptosis, excitotoxicity, huntingtin aggregation, huntingtin proteolysis, huntingtin phosphorylation, inflammation, oxidative damage, phosphodiesterase activity, histone deacetylase inhibitors, and transglutaminase activity as well as compounds that modulate mitochondrial function, chaperone activity,transcription, and neurotrophic support. Therapeutics that have shown improvements in mouse models of HD and are in preliminary trials include minocycline, sodium butyrate, essential fatty acids, racemide, creatine, cystamine, riluzole, and memantine.[68,69,70] Several gene silencing therapies are being developed, including approaches using RNA interference (RNAi) or antisense-oligonucleotides (ASOs).[70,71] Some methods aim to silence all huntingtin expression, while others are allele-specific and aim to target only the pathogenic variant, leading to personalized therapy for HD. Neural transplantation studies in HD have shown variable results with small numbers of individuals.[72] However additional larger studies are underway. Of concern, recent studies suggest that mutant huntingtin is capable of spreading into the allografted neural tissue. Biomarker studies, such as TRACK-HD, PREDICT-HD and ENROLL-HD, are/have been conducted to identify early changes in disease progression using imaging, clinical scales, and physiologic measurements. Longitudinal studies of persons at risk for HD have also been performed.[73,74]

Lifestyle and Home Remedies

Managing Huntington's disease is demanding on the person with the disorder, family members and other in-home caregivers. As the disease progresses, the person will become more dependent on caregivers. A number of issues will need to be addressed, and strategies to cope with them will evolve.

Eating and Nutrition

Factors regarding eating and nutrition include the following:

➢ People with Huntington's disease often have difficulty maintaining a healthy body weight**.** Difficulty eating, higher caloric needs due to physical exertion or unknown metabolic problems may be the cause. To get adequate nutrition, more than three meals a day may be necessary.

➢ Difficulty with chewing, swallowing and fine motor skills can limit the amount of food patients eat and increase the risk of choking. Problems may be minimized by removing distractions during a meal and selecting foods that are easier to eat. Utensils designed for people with limited fine motor skills and covered cups with straws or drinking spouts also can help.[75]

Eventually, a person with Huntington's disease will need assistance with eating and drinking.

Managing Cognitive and Psychiatric Disorders

Family and caregivers can help create an environment that may help a person with Huntington's disease avoid stressors and manage cognitive and behavioral challenges. These strategies include:

➢ Using calendars and schedules to help keep a regular routine

➢ Initiating tasks with reminders or assistance

➢ Prioritizing or organizing work or activities

➢ Breaking down tasks into manageable steps

➢ Creating an environment that is as calm, simple and structured as possible

➢ Identifying and avoiding stressors that can trigger outbursts, irritability, depression or other problems

➢ For school-age children or adolescents, consulting with school staff to develop an appropriate individual education plan[76]

➢ Providing opportunities for the person to maintain social interactions and friendships as much as possible.

Support Services

Support services for people with Huntington's disease and families include the following:

➢ Nonprofit agencies**,** such as the Huntington's Disease Society of America, provide caregiver education, referrals to outside services, and support groups for people with the disease and caregivers.

➢ Local and state health or social service agencies may provide daytime care for people with the disease, meal assistance programs or respite for caregivers.[77]

Planning for Residential and End-Of-Life Care:

Because Huntington's disease causes the progressive loss of function and death, it's important to anticipate care that will be needed in the advanced stages of the disease and near the end of life. Early discussions about this type of care enable the person with Huntington's disease to be engaged in these decisions and to communicate his or her preferences for care.

Creating legal documents that define end-of-life care can be beneficial to everyone. They empower the person with the disease, and they may help family members avoid conflict late in the disease progression. Doctor can offer advice on the benefits and drawbacks of care options at a time when all choices can be carefully considered.[78]

Matters that may need to be addressed include:

➢ *Care facilities*

Care in the advanced stages of the disease will likely require in-home nursing care or care in an assisted living facility or nursing home.

➢ *Hospice care.*

Hospice services provide care at the end of life that helps a person approach death with as little discomfort as possible. This care also provides support and education to the family to help them understand the process of dying.

➢ *Living wills.*

Living wills are legal documents that enable a person to spell out care preferences when he or she isn't able to make decisions. For example, these directions might indicate whether or not the person wants life-sustaining interventions or aggressive treatment of an infection.

➤ *Advance directives*

These legal documents enable one to identify one or more people to make decisions on their behalf. One may create an advance directive for medical decisions or financial matters.

Prevention[79-81]

People with a known family history of Huntington's disease are understandably concerned about whether they may pass the Huntington gene on to their children. These people may consider genetic testing and family planning options. If an at-risk parent is considering genetic testing, it can be helpful to meet with a genetic counselor. A genetic counselor will discuss the potential risks of a positive test result, which would indicate the parent will develop the disease. Also, couples will need to make additional choices about whether to have children or to consider alternatives, such as prenatal testing for the gene or in vitro fertilization with donor sperm or eggs.[80] Another option for couples is in vitro fertilization and preimplantation genetic diagnosis. In this process, eggs are removed from the ovaries and fertilized with the father's sperm in a laboratory. The embryos are tested for presence of the Huntington gene, and only those testing negative for the Huntington gene are implanted in the mother's uterus.

Future Perspectives

Huntington's disease is a physically, psychologically and socially devastating disorder. Knowledge about the disease and care for patients has increased enormously over the last two decades. As the mean duration of illness is more than 17 years, one tends to forget the many years prior to the onset of symptoms during the at-risk and the preclinical periods, or the premanifest period. Huntington's disease is a lifelong disease for both the individual and the family. From the moment the gene was localized in 1983, and particularly after 1993, attention has focused on the pathophysiological pathway with the aim of developing a therapy.

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. Drugs that can slow down, delay, or stop the onset of the disease are being sought. 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 the search for biomarkers, a very well organised study is underway: TRACK-HD, a multinational study with 366 participants. This will end in 2011.[81] The Registry study, the main project of the European Huntington Disease Network, also aims to prepare the field for larger studies when drugs become available for human testing. In parallel with the rational pathway to find solutions to treat this disorder, attention is being paid to finding the best care for all patients and at-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.

CONCLUSION

Considerable data are now available regarding early indicators of HD that are detectable years (if not decades) before traditional clinical diagnosis. Usage of any one of the multiple measures reported here results in earlier detection of the pathophysiology of HD. It is important to understand what these findings may mean in the context of clinical care and research. First, the time course for HD has at least doubled. Second, these efforts to detect earlier disease have resulted in a more comprehensive characterization of HD. What was once a traditional movement disorder is now better described with three key features of basal ganglia functions: movement, cognitive and psychiatric disturbances. Finally, and perhaps most urgently, it is evident that the pathophysiology of HD starts long before the point at which the criteria for traditional diagnosis are satisfied.
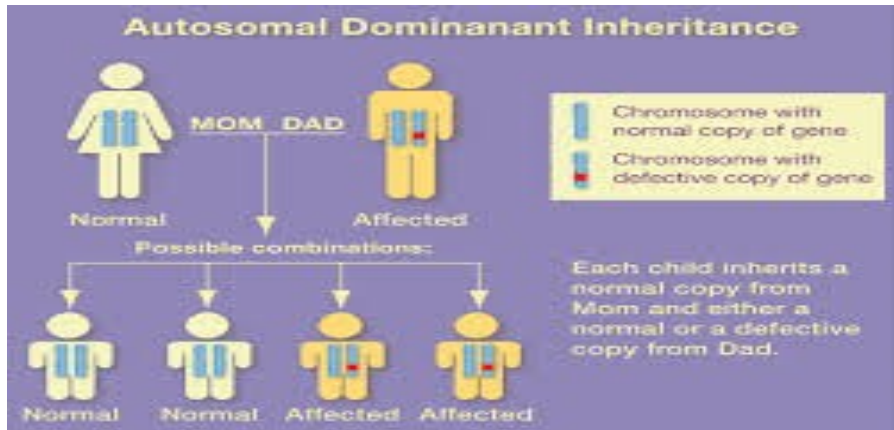
Figure 1: Brain Diagram Describing Huntington's Disease[6]
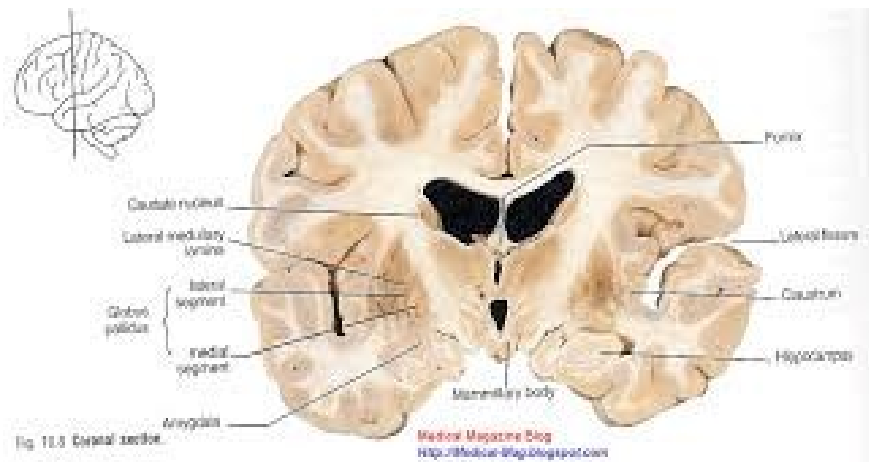

Figure 2: Genetics of HD[16]

Figure 3: Huntington's disease cause-symptoms[30]

Figure 4: There appears to be a ray of hope for patients with Huntington's disease, which is a rare inherited genetic disorder[63]

Nature Reviews | Neuroscience

Figure 5: Experimental therapeutics in transgenic mouse models of Huntington's disease[69]

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