A Review on Current Prospect of Huntington’s Disease

Keywords: Hormonal, Neurodegenerative, Choreatic, Huntington, Hereditary

ABSTRACT

Huntington’s disease is an inherited disease that causes the progressive dying off, or degeneration, of nerve cells in certain parts of the brain. HD is a rare neurodegenerative disorder of the central nervous system characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia, cognitive and motor. The disease occurs in all racial group but most common in people of northern European origin. Its prevalence in the western hemisphere is 7-10/10000. 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 (Juvenile Huntington's disease; JHD). HD is an autosomal dominant inherited disease caused by an elongated CAG repeat (36 repeats or more) on the short arm of chromosome in the Huntington gene, the number of CAG repeats is related to how much this process is affected, and accounts for about 60% of the variation of the age of the onset of symptoms. A diagnosis of Huntington’s disease is generally based on findings from neurological, psychological, and genetic testing. A number of medications may be prescribed to help control emotional and movement problems associated with HD. It is important to remember however, that while medicines may help keep these clinical symptoms under control, there is no treatment to stop or reverse the course of the disease. Chorea is treated with dopamine receptor blocking or depleting agents. Management should be multidisciplinary and is based on treating signs and 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. The most common cause of death is pneumonia, followed by suicide. We continue to learn about how to improve our services from our patients and their families. In the future treatments might be initiated in the premanifest phase, with the hope of delaying or halting the disease process itself.
INTRODUCTION:

Huntington’s disease is inherited diseases that cause the progressing dying off, or degenerations, of nerve cells in certain part of the brain. American physicians George Huntington wrote the first thorough description of Huntington’s disease (HD) in 1872, calling it “hereditary chorea”. Chorea is derived from the Greek word for dance and describes the uncontrollable dance-like movements seen in people with HD. The hereditary nature of HD helps distinguish it from other types of chorea with infectious, metabolic, or hormonal causes. Understanding the hereditary nature of HD eventually enabled modern researchers to pinpoint the cause of the disease- a mutation or misspelling in a single gene. The disease occurs in all racial group but most common in people of northern European origin. Its prevalence in the western hemisphere is 7-10/10000. 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 (Juvenile Huntington's disease; JHD). Symptoms of HD most commonly become noticeable between the ages of 35 and 44 years, but they can begin at any age from infancy to old age. In the early stages, there are subtle changes in personality, cognition, and physical skills. The physical symptoms are usually the first to be noticed, as cognitive and behavioral symptoms are generally not severe enough to be recognized on their own at the earlier stages. Almost everyone with HD eventually exhibits similar physical symptoms, but the onset, progression and extent of cognitive and behavioral symptoms vary significantly between individuals. Common symptoms of HD are motor symptoms, cognitive symptoms, psychiatric symptoms, metabolic symptoms, suicide risk, etc.

Genetics:

All humans have two copies of the Huntington gene (HTT), which codes for the protein Huntington (HTT). The gene is also called HD and IT15, which stands for ‘interesting transcript 15’. Part of this gene is a repeated section called a trinucleotide repeat, which varies in length between individuals and may change length between generations. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant Huntington protein (mHTT). The differing functions of these proteins are the cause of pathological changes which in turn cause the disease symptoms. Huntington's disease mutation is genetically dominant and
almost fully penetrant: mutation of either of a person's HTT alleles causes the disease. It is not inherited according to sex, but the length of the repeated section of the gene and hence its severity can be influenced by the sex of the affected parent.

Genetic mutation

HD is one of several trinucleotide repeat disorders which are caused by the length of a repeated section of a gene exceeding a normal range. The HTT gene is located on the short arm of chromosome 4 at 4p16.3. HTT contains a sequence of three DNA bases—cytosine – adenine guanine (CAG)—repeated multiple times (i.e. ... CAGCAGCAG ...), known as a trinucleotide repeat. CAG is the 3-letter genetic code (codon) for the amino acid glutamine, so a series of them results in the production of a chain of glutamine known as a polyglutamine tract (or polyQ tract), and the repeated part of the gene, the PolyQ region.

Classification of trinucleotide repeats, and resulting disease status, depends on the no of CAG repeats:

<table>
<thead>
<tr>
<th>Repeat count</th>
<th>classification</th>
<th>Disease status</th>
<th>Risk to offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;27</td>
<td>Normal</td>
<td>Will not be affected</td>
<td>None</td>
</tr>
<tr>
<td>27-35</td>
<td>Intermediate</td>
<td>Will not be affected</td>
<td>Elevated, but &lt;50%</td>
</tr>
<tr>
<td>36-39</td>
<td>Reduced penetrance</td>
<td>May or may not be affected</td>
<td>50%</td>
</tr>
<tr>
<td>40+</td>
<td>Full penetrance</td>
<td>Will be affected</td>
<td>50%</td>
</tr>
</tbody>
</table>

Generally, people have fewer than 36 repeated glutamines in the polyQ region which results in production of the cytoplasmic protein Huntington. However, a sequence of 36 or more glutamines results in the production of a protein which has different characteristics. This altered form, called mutant Huntington (mHTT), increases the decay rate of certain types of neurons. Regions of the brain have differing amounts and reliance on these types of neurons and are affected accordingly. Generally, the number of CAG repeats is related to how much this process is affected, and accounts for about 60% of the variation in the age of the onset of symptoms. The remaining variation is attributed to environment and other genes that modify the mechanism of HD. 36–39 repeats result in a reduced penetrance form of the disease, with a much later onset and slower progression of symptoms. In some cases, the onset may be so late that symptoms are never noticed. With very large repeat counts, HD has full penetrance and can occur under the age of 20, when it is then referred to as juvenile HD, akinetic-rigid, or Westphal variant HD. This accounts for about 7% of HD carriers.
Inheritance:

As a genetic disease HD is recognized as a dominantly inherited disorder, meaning that only of the two for genes for the protein Huntington needs to contain the disease causing mutation for HD to develop. This also means that each child of a person with HD has a 50 percent chance of inheriting the defective gene and developing the disease. Men and women are at equal risk. Because individual carrying the HD gene may not realize the disease runs in child family, they sometimes do not learn that they will get HD until after they have had children, unknowingly placing their children at 50-50 risk present, and to do this efficiency without causing side effects is very challenging. So instead of targeting the mutant protein itself for destruction, researchers chose to focus on its Ribonucleic acid (RNA), because various technologies were being developed to permit the efficient and specific targeting of RNA molecules, even in the brain. (Recall that the DNA sequence, or deoxyribonucleic acid sequence, of each gene is transcribed into a molecule of messenger RNA [mRNA], whose triplets’ code for amino acid that are translated into the gene’s protein).

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).

Pathophysiology:

In Huntington disease, the caudate nucleus atrophies, the inhibitory medium spiny neurons in the corpus striatum degenerate, and levels of the neurotransmitters gamma-amino butyric acid (GABA) and substance P decrease. HD is a progressive, fatal neurological condition caused by an expansion of CAG (glutamine) repeats in the coding region of the Huntington gene. To date, there is no cure but great strides have been made to understand pathophysiological mechanisms. In particular, genetic animal models of HD have been instrumental in elucidating the progression of behavioral and physiological alterations, which had not been possible using classic neurotoxin models.

Striatum (located in basal ganglia) is most affected by HD.

Motor control operates through three pathways:
1. Direct pathway

2. Indirect pathway

3. Striatonigral pathway

**How does HD affect the brain?**

The most severe loss of nerve cells (also called neurons) occurs in deep brain structures called the basal ganglia, especially in a part of the basal ganglia called the striatum. The basal ganglia have a variety of functions, including helping to control voluntary (intentional) movement. Subsections of the basal ganglia, called the caudate nuclei and putamen, are most severely affected. Another strongly affected area is the brain’s outer surface, or cerebral cortex, which has important roles in movement, as well as thought, perception, memory, and emotion.

As HD progresses over time, neuronal degeneration becomes more widespread throughout the brain. In addition to metabolic changes, there is degeneration in areas of the brain that control hormones.

**Diagnosis:**

A diagnosis of Huntington’s disease is generally based on findings from neurological, psychological, and genetic testing.

**Neurological tests:** A neurologist will interview the individual intensively to obtain medical history and rule out other conditions. Tests of neurological and physical functions may review reflexes, balance, movement, muscle tone, hearing, walking, and mental status. A number of 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. It is extremely important for family members to be candid and truthful with a professional who is taking a family history since another family member(s) may not have been accurately diagnosed with the disease but thought to have other issues.
**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, doctors may try to get a clearer picture of disease risk by asking other family members to come in for examination and genetic testing.

Prior to the availability of the direct genetic test, clinics used a method called linkage testing. This older method requires a sample of DNA from a closely related affected relative, preferably a parent, for the purpose of identifying markers close to the HD gene. A version of the linkage method is sometimes still used for prenatal testing.

**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.

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

**Treatments:**

A number of medications may be prescribed to help control emotional and movement problems associated with HD. It is important to remember however, that while medicines may help keep these clinical symptoms under control, there is no treatment to stop or reverse the course of the disease.

Most of the medications available for HD symptoms work by modulating neurotransmitters—the chemical messages that shuttle between neurons. For many of these drugs, their mechanisms of action against HD are not fully understood.
Tetrabenazine, which causes depletion of the neurotransmitter dopamine, is prescribed for treating Huntington’s-associated involuntary movements, as is deutetrambenazine.

Antipsychotic drugs, such as risperidone, olanzapine, or haloperidol, or other drugs such as clonazepam, may help to alleviate choreic movements and may also be used to help control hallucinations, delusions, and violent outbursts. Antipsychotic drugs, however, typically do not help with the muscle contractions associated with dystonia (involuntary muscle contractions that can cause slow, repetitive movement or abnormal postures), and may in fact worsen the condition, causing stiffness and rigidity.

For depression, physicians may prescribe citalopram, fluoxetine, sertraline, nortriptyline, or other compounds. Tranquilizers can help control anxiety and lithium may be prescribed to combat pathological excitement and severe mood swings.

Drugs used to treat the symptoms of HD may have side effects such as fatigue, sedation, decreased concentration, restlessness, or hyperexcitability, and should be only used when symptoms create problems for the individual. For those on medication, it may be difficult to tell if a particular symptom, such as apathy or memory loss, is a sign of the disease or a drug react.

**Depression**

Depression is extremely common in HD and occurs as an intrinsic feature of the disease rather than merely as a response to being diagnosed with an incurable disease.

Treatment is with standard antidepressant medications. While there is not an established evidence base for the treatment of depression in HD, our experience is that antidepressants are frequently very effective, (Novak and Tabriz). An SSRI such as citalopram is generally used as first line treatment, though stimulating SSRIs such as fluoxetine should be avoided as they can cause hyper stimulation and exacerbate anxiety, both of which are common in HD. If insomnia is a problem, a sedating antidepressant at night instead (e.g. mirtazapine) can be useful. Psychological therapies, such as CBT, can also be helpful in well-selected patients, and support from local community mental health teams is often invaluable.

Antidepressants include drugs such as citalopram (Celexa), escitalopram (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.

**SYMPTOMATIC MANAGEMENT OF PSYCHIATRIC SYMPTOMS IN HUNTINGTON’S DISEASE**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug Class</th>
<th>Medication</th>
<th>Main Adverse Effects and Treatment Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>Atypical neuroleptics</td>
<td>Olanzapine, Risperidone, Quetiapine</td>
<td>See above. Careful use in the elderly where there is increased risk of stroke with olanzapine and risperidone</td>
</tr>
<tr>
<td>Treatment-resistant psychosis</td>
<td>Neuroleptics</td>
<td>Clozapine</td>
<td>As for the other neuroleptics, plus agranulocytosis, myocarditis and Cardiomyopathy. Requires blood monitoring</td>
</tr>
<tr>
<td>Psychosis with prominent negative symptoms</td>
<td>Neuroleptics</td>
<td>Aripiprazole</td>
<td>Parkinsonism, akathisia, drowsiness, GI disturbance, tremor, blurred vision</td>
</tr>
<tr>
<td>Depression, anxiety, OCB, irritability,</td>
<td>Selective serotonin</td>
<td>Citalopram</td>
<td>GI disturbance, hypersensitivity reactions, drowsiness, syndrome of inappropriate antidiuretic hormone secretion (SIADH), postural hypotension</td>
</tr>
<tr>
<td>aggression</td>
<td>reuptake inhibitors (SSRI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered sleep-wake cycle</td>
<td>Hypnotics</td>
<td>Zopiclone Zolpidem</td>
<td>Drowsiness, confusion, memory disturbance, GI disturbance</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Anticonvulsants</td>
<td>Lamotrigine</td>
<td>Hypersensitivity reactions, blood dyscrasias, dizziness, GI disturbance, depression</td>
</tr>
</tbody>
</table>

**Anxiety**

Anxiety is also common in HD but can respond to treatment with no stimulating **SSRIs**, **buspirone** or **benzodiazepines**.

**Apathy**

Patients suffering from apathy can find it particularly difficult to initiate activities but are often able to participate fully with encouragement and support once they get started on things.

**Obsessive-compulsive behaviors and perseveration**

Obsessive-compulsive thoughts and behaviors are also relatively common in HD.
Mood-stabilizing drugs that can help prevent the highs and lows associated with bipolar disorder include anticonvulsants, such as divalproex (Depakote), carbamazepine (Carbatrol, Epitol, others) and lamotrigine (Lamictal).

Sexuality

Sexuality often remains unchanged in HD, though it is also common for sex drive to decline. It is also important to remember that many patients with HD are on medications such as SSRIs which can cause sexual dysfunction; these should be reviewed if sexual dysfunction is a problem.

Swallowing problems

Eventually, patients may become unable to swallow anything safely and PEG insertion may be considered. This is often a highly emotive subject and the issue should be raised with patients and their carers while patients are still able to eat to avoid crisis point being reached. PEG insertion does reduce the risk of aspiration but patients may choose not to have this. It may be the subject that triggers a patient to make an advanced directive; a significant number of individuals decide against PEG insertion and planning in advance with an advanced directive can be invaluable in avoiding the need to discuss this when disease has advanced to the point when patients are unable to communicate and a decision is needed urgently. This is discussed in more detail in the section on advanced disease and end of life issues.

Psychotherapy

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

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 your ability to speak clearly or teach you to use communication devices — such as a board covered with pictures of everyday items and activities. Speech therapists can also address difficulties with muscles used in eating and swallowing.
Physical therapy

A physical therapist can teach you 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, 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.

Management including treatment

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. Surgical treatment does not play an important role in HD.
Looking to the future: Research into new treatments for Huntington’s disease

At the time of writing, there is a major drive to find disease-modifying and new symptomatic treatments for HD; many new developments have been made in recent years, and phase 3 trials are ongoing (Novak and Tabrizi, 2010). Much progress has also been made in developing and evaluating sensitive biomarkers which will help to measure the effects of disease modifying therapies in future clinical trials, particularly in the premanifest and early stages of the disease (Paulsen 2008; Tabrizi 2009).

Future disease modifying treatments will, in practice, probably comprise a combination of compounds which will target several key pathogenic pathways to achieve optimal effect. This approach is similar to that used in the treatment of HIV or cancer. Some potential therapeutic strategies are summarized below (Ross and Tabrizi, 2011).

* Enhancing clearance of mutant Huntington by cellular clearance mechanisms: a number of compounds being tested in mouse models of HD aim to promote clearance of the mutant protein, Huntington, which is generated by the expanded HTT gene.

* Histone deacetylase inhibitors: these target the transcriptional dysregulation that occurs early in HD pathogenesis.

* Inhibitors of proteolytic cleavage of full-length mutant Huntington to prevent production of the potentially toxic N-terminal fragment.

* Gene silencing: switching off expression of the mutant gene itself.

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. It was the first autosomal dominant disease where premanifest diagnosis became possible and it was the first trinucleotide disease to be described. Consequently, since 1993
many researchers have developed an interest in this disorder. The number of publications has increased enormously.

What is the current perspective? 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 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.

**Clinical studies:**

Studies of cognition, emotional functioning, and movement, studies of motor problems (abnormal eye movements, chorea, and dystonia), psychiatric symptoms (apathy, psychosis, depression, and irritability), and tests of cognitive skills (learning and memory, attention, concentration, and executive functioning such as multitasking, problem-solving, and planning) may serve to identify when the symptoms of HD appear and help characterize their range and severity as the disease progresses over time.

Clinical trials of drugs, testing investigational drugs may lead to new treatments and at the same time improve our understanding of the disease process in HD. Classes of drugs being tested include those that control symptoms, slow the rate of progression of HD, block the effects of excitotoxins, provide support factors that improve neuronal health, or suppress metabolic defects that contribute to the development and progression of HD.

Imaging. Various imaging technologies allow investigators to view changes in the volume and structures of the brain, and to pinpoint when these changes occur in HD. Positron emission tomography (PET, which visualizes metabolic or chemical abnormalities in the brain) allows scientists to learn how HD affects the chemical systems of the brain. Investigators hope to learn if PET scans can reveal abnormalities that signal HD, as well as to characterize neurons that have died and chemicals that are depleted in parts of the brain of people with HD. Investigators are using functional MRI (fMRI), a form of magnetic resonance imaging that measures changes in the flow of blood-born chemicals known to
correlate with brain activity, to understand how HD affects the functioning of different regions of the brain.

Brain structure- Altered brain development may play an important role in HD. Huntington is expressed during embryonic development and throughout life. Studies in animals have shown that the normal HD gene is vital for brain development. Adults who carry the mutant HD gene but have not yet displayed symptoms of the disease show measurable changes in the structure of their brain, even up to 20 years before onset of clinical diagnosis. It is not known when in life these changes become evident. One possibility is that the HD gene causes changes in early brain development that remain throughout life, and initially cause only subtle functional abnormalities.

CONCLUSION:

Managing the many facets of Huntington’s disease can be challenging and is best served within multidisciplinary settings. We continue to learn about how to improve our services from our patients and their families. In the future treatments might be initiated in the premanifest phase, with the hope of delaying or halting the disease process itself. Huntington’s disease is a progressive neurodegenerative genetic disorder in chromosome 4 of human being. Loss of brain neurons causes the clinical manifestation of diseases. It is severe diseases that affect quality of life and survival. Unfortunately, the diseases is incurable. HD is a progressive and devastating disease. Over the last decade there has been a rapid growth in our understanding of the natural history of HD and pathogenesis at both the cellular and macroscopic level. To date few treatments are available and a number of clinical trials have failed. However, the development of therapeutic strategies capable of targeting mHTT directly heralds a new era for HD research. Now more than ever there is a real potential to modify and prevent HD.

REFERENCES:


