Symptomatic Treatment and Management of Huntington’s Disease: An Overview

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Abstract: Huntington’s disease (HD) is an inherited disease of the central nervous system that usually has its onset between 30 and 50 years of age. The patient has progressive dementia with bizarre involuntary movements of chorea. The disease slowly progresses and death is usually due to an intercurrent infection. Huntington’s disease affects someone’s ability to think, talk and move by destroying cells in the basal ganglia, the part of the brain that controls these capacities. A patient with Huntington’s disease may present with neurological or psychiatric symptoms, or both. The movement disorder may begin with simple twitching or jerking or with clumsiness or coordination problems. Huntington’s disease caused by the expansion of the polyglutamine tract in the N-terminus of the HD protein (Huntingtin). Although there is currently no cure for this disease, there are ways to manage symptoms effectively. Symptomatic treatment of Huntington’s disease involves use of Dopamine antagonists, presynaptic dopamine depleters, Antidepressants, Tranquillizers, Anxiolytic Benzodiazepines, Anticonvulsants and Antibiotics. Several medications including baclofen, idebenone and vitamin E have studied in clinical trials with limited samples. In the present article, we have concentrated on clinical features, diagnosis, symptomatic approaches and other possible therapies involved in the management of Huntington’s disease. The aim of present article is to provide in depth knowledge about symptomatic treatment and other therapies involved in the management of Huntington’s disease. This article reviews current therapeutic agents for treatment of the symptoms of Huntington’s disease.

Key words: Chorea • Huntington’s • Management • Dystonia • Bradykynesia

INTRODUCTION

Chorea is the rapid, jerky, dyskinetic, irregular, purposeless, arhythmic and asymmetric movements that occur both at rest and during voluntary movements. It is a nervous condition marked by involuntary muscular twitching of the limbs or facial muscles. Chorea affects different parts of the body at irregular intervals. A variety of different disease processes can lead to the development of chorea. Huntington’s chorea or disease is a progressive, autosomal and inherited disorder of the central nervous system characterized by widespread degenerative changes of the cerebral cortex, basal ganglia and other brain regions and the development of prominent chorea and dementia. Other types of movement disorders also occur in this disease including dystonia, bradykynesia and cerebellar dysfunction. Chorea, which dominates during the early stages, can be replaced by dystonia and bradykynesia late in the disease [1].

Huntington’s disease results from genetically programmed degeneration of brain cells called neurons, in certain areas of the brain. This degeneration causes uncontrolled movements and emotional disturbance. Huntington’s disease is a familial disease hereditary from parent to child through a gene mutation that leads to a toxic accumulation of protein in the brain. Huntington’s disease inherited from either one or both parents. Although this disease inherited either from mother or father or both, characterized by loss of neurons from the neostriatum, which is the principal input structure of the basal ganglia [2].

Huntington’s disease is a neurodegenerative disorder characterized by midlife onset, involuntary movements, cognitive decline and behavioral disturbances. It is the
commonest of a group of so-called ‘trinucleotide-repeat’ neurodegenerative diseases, associated with expansion of the number of repeats of the CAG sequence in specific genes and hence the number (50 or more) of consecutive glutamine residues in the expressed protein. The larger the number of repeats of the CAG sequences in specific genes, the earlier the appearance of symptoms. Studies on post mortem brains showed that the dopamine content of the striatum was normal or slightly increased. It show that the loss of GABA-mediated inhibition in the basal ganglia produces a hyperactivity of dopaminergic synapses, so the syndrome is in some senses a mirror image of Parkinson’s disease [3].

The development of Huntington’s chorea seems to be related that an imbalance of dopamine, acetylcholine, GABA and perhaps other neurotransmitters in the basal ganglia. Pharmacologic studies indicate that chorea results from over activity in dopaminergic nigrostriatal pathways perhaps because of increased responsiveness of postsynaptic dopamine receptors. Both GABA and the enzyme glutamic acid decarboxylase concerned with its synthesis markedly reduced in the basal ganglia of patients with Huntington’s disease. There is also a significant decline in concentration of choline acetyltransferase, the enzyme responsible for synthesizing acetylcholine in ganglia of these patients [4].

Huntington’s disease is characterized by prominent neuronal loss in the caudate/putamen of the brain [5, 6, 7]. The brain in Huntington’s disease is usually small, offer weighing less than 1100 gm. The areas of the brain such as fewer neurons in cerebral cortex, hypothalamus and thalamus are affected in the Huntington’s disease. Interneurons and afferent terminals are largely spared, while the striatal projection neurons are severely affected. This leads to large decreases in striatal gamma amino butyric acid concentrations, but somatostatin and dopamine concentrations are relatively preserved [8, 9].

The researchers suggested that the Huntington’s disease occur by trinucleotide repeats in the Huntington gene, which cause, in turn, the synthesis of a form of the Huntington protein containing an abnormal number of glutamine residues. The normal Huntington contains between 6 and 34 copies of CAG sequence but in Huntington’s disease, the number of triplet repeats is increased which carrying between 40 and 55 CAG copies. The larger the numbers of trinucleotide repeats, the earlier the onset of disease and the patients carry greater than 70 CAG copies known as Juvenile-onset Huntington’s disease. Before the development of symptoms, affected patients identified by the demonstration of excessive CAG repeats in responsible gene [10].

Signs and Symptoms of Huntington’s Disease [11-13]:
Because Huntington’s disease affects the mind, body and emotions, symptoms often mimic other conditions. The general symptoms in early stages can include poor memory; difficulty making decisions; mood changes such as increased depression, anger or irritability; a growing lack of coordination, twitching or other uncontrolled movements; difficulty walking, speaking and swallowing. The order in which symptoms develop will vary from person to person. As the disease continues, the symptoms become progressively worse and lead to incapacitation. The summaries of different type of symptoms are summarized below:

Physical Symptoms: Physical symptoms include chorea (involuntary movements of the limbs, face and body). Chorea may lead to difficulty walking, speaking and swallowing. Choking is a particular hazard, due to reduced ability to control the muscles of the tongue, neck and diaphragm. People often lose weight because they have difficulty eating and burn more calories due to the continuous movement. The physical symptoms are given as:

- Development of tics (involuntary movement) in the fingers, feet, face, or trunk
- Increased clumsiness
- Loss of coordination and balance
- Slurred speech
- Jaw clenching or teeth grinding
- Difficulty swallowing or eating
- Continual muscular contractions.
- Stumbling or falling.

Cognitive or Mental Symptoms: Over time, these symptoms may progress to a stage where the person loses the ability to recognize familiar objects, people and places. Cognitive symptoms include a loss of drive and initiative. People with Huntington’s disease may appear to be lazy or uninterested in life, spending days doing little, or neglecting personal hygiene. They may also lose the ability to organize themselves, as planning skills and ability to carry out more than one task at once deteriorate. In later stages, people may get memory loss and be less able to understand speech. Memory affected, but affected persons rarely lose their memory of family, friends and the immediate situation. The following cognitive or mental symptoms as follows:

- Decreased concentration
- Forgetfulness and memory decline
- Poor judgment
- Difficulty making decisions or answering questions
- Difficulty driving

**Emotional Symptoms:** Initial emotional symptoms are usually slight and thus easy to misinterpret. Many conditions and life circumstances can trigger mood changes, so it is especially important to know what psychiatric signs may indicate Huntington’s disease. Depression, the most common psychiatric symptom of Huntington’s disease will generally manifest as:

- Hostility/irritability
- Lack of energy
- Ongoing disinterest in life (lack of pleasure or joy)
- Bipolar disorder (manic-depression) in some Huntington’s disease patients

Emotional symptoms include depression, not only because of the burden of having a progressive disorder, but also as a direct result of the damage to certain brain cells. People often become frustrated at being unable to work or carry out previously simple tasks. They also seem to behave stubbornly, probably due to a reduced ability to react flexibly and to understand the needs and emotions of others. People with Huntington’s disease may also become more irritable and antisocial than usual. Such persons often become irritable, anxious and depressed that is why common causes of death include suicide and intercurrent infections.

A person with Huntington’s disease may eventually begin to exhibit psychotic behavior such as:

- Delusions
- Hallucinations
- In-appropriate behavior (e.g., unprovoked aggression)
- Paranoia

The outcome of Huntington’s disease is invariably fatal; over a course of 15 to 30 years, the affected person becomes totally disabled and unable to communicate requiring full time care; death ensues from the complications of immobility.

**Diagnosis [14]:** DNA analysis can be used to confirm the diagnosis. Tests are available to identify whether someone has the faulty gene. Genetic testing can diagnose Huntington’s disease at every stage of the life cycle. There are three categories for testing such as: antenatal or prenatal, pre-symptomatic and confirmatory testing.

**Antenatal or Prenatal Testing:** Either amniocentesis (a sample of fluid from around the fetus), or chorionic villus sampling (CVS)-a sample of fetal cells from the placenta will indicate whether the body has inherited the gene for Huntington’s disease. Antenatal tests are carried out early in pregnancy on the unborn children of couples from families affected by Huntington’s disease. They can be used to calculate the risk of that child going on to develop the disease in their adult life. Again, the implications of positive results are serious and couples need advice and support from a specialist doctor or counselor to help them in their decisions.

**Pre-symptomatic Testing:** These are available to the people who are at risk of inheriting Huntington’s disease from a parent, but do not have symptoms and don’t know whether or not they carry the gene. Pre-symptomatic tests are carried out in people who are not showing symptoms of Huntington’s disease, but have a family history of it. The decision to take a test is a serious one: a positive result can be devastating since it tells the individual that they will one day become severely mentally ill. There are also issues surrounding testing when the individual parents have themselves not been tested, since a positive result indicates that one parent also has the faulty gene. Advice from a genetic counselor about the implications of taking the test is needed before going ahead.

**Confirmatory Testing:** This determines whether a person showing what appear to be the symptoms of Huntington’s disease, actually has the disease. Neurological and psychological tests are also conducted to arrive at a conclusive diagnosis of Huntington’s disease.

**Pre-Symptomatic Testing Is Usually Recommended When:**

- A parent is known to have, or is suspected of having Huntington’s disease
- An at-risk parent is still living, but doesn’t know whether they carry the Huntington’s gene

If someone’s grandparent has Huntington’s disease but the parent does not know his or her carrier status, the grandchild has a one in four chance of developing the
disease. This can be an emotionally charged issue, because revealing the tested individual’s Huntington’s disease status also reveals whether or not their parent carries the gene. It is therefore crucial to discuss the testing option with family members who will be affected by the outcome. Testing asymptomatic children under age 18 presents a similarly controversial issue. It is generally recommended that pre-symptomatic children not be tested until they can manage this decision for themselves. Parental consent must be given if an under-age child is tested. Usually a neurological examination is carried out before pre-symptomatic testing to confirm that an individual has not already developed the disease.

Symptomatic Treatment and Management [15-21]:
The emphasis today is on living positively with Huntington’s disease. An integrated, multi-disciplinary approach focuses on the triad of:

- Diet and supplements
- Exercise
- Spiritual and psycho-social support

This well-rounded program enhances quality of life for people living with Huntington’s disease as well as for those at risk of developing Huntington’s disease and may very likely delays the onset of symptoms. Foods known to nourish the brain, support memory and build overall immunity are especially recommended. Once Huntington’s disease is confirmed, patients are encouraged to continue this approach, adding other health support therapies, as they become necessary including physical, occupational and speech therapy.

Most people who have Huntington’s disease eventually become physically and mentally disabled. As the disease progresses, long-term nursing home care may be necessary. Because Huntington’s disease has no known cure, treatment is supportive, protective and aimed at relieving symptoms. It is extremely important for people with Huntington’s disease to maintain physical fitness as much as possible, as individuals who exercise and keep active tend to do better than those who do not. No satisfactory treatment is available to stop or reverse Huntington’s disease, but some approaches can control signs and symptoms. Medications are available to treat the symptoms of Huntington’s disease. Treatments include medication, mental health care, other therapies (speech, swallowing and physical therapies) and family support.

[A] Medication: No medications are approved by the Food and Drug Administration (FDA) to treat the symptoms of Huntington’s disease. However, some medications approved to treat other conditions have worked for some patients. Physicians prescribe a number of medications to help control emotional and movement problems associated with Huntington’s disease. Most drugs used to treat the symptoms of Huntington’s disease have side effects such as fatigue, restlessness, or hyperexcitability. Many drugs are being studied to determine if they slow the progression of Huntington’s disease, but currently no drug has been recommended. To decrease chorea, doctors may prescribe tranquilizers such as dopamine antagonists, dopamine depletors, or clonazepam. These drugs have side effects (such as worse balance, more difficulty swallowing and exacerbation of depression) that must be weighed against their benefits. SSRIs (Serotonin specific re-uptake inhibitors) antidepressants, mood stabilizers, or neuroleptics may also be prescribed in coordination with psychiatric counseling to address psychological problems. Practical treatment for symptomatic Huntington’s disease emphasizes the selective use of medications. The symptomatic treatment of Huntington’s disease may be outlined as follows:

**Dopamine Antagonists:** Dopamine antagonists are effective in reducing the involuntary movements. Haloperidol, pimozide and sulphiride are the most frequently used dopamine antagonists in the treatment of movement disorders like chorea as observed in Huntington’s disease.

**Presynaptic Dopamine Depleters:** Tetrabenazine is presynaptic dopamine depleters, which acts on neurons to deplete synaptic vesicles of dopamine and other monoamines. It causes the release of dopamine from synaptic vesicles and blocks its uptake into the vesicles. Tetrabenazine produces a decrease in the content and activity of dopamine, norepinephrine and serotonin in the brain. It also acts to block postsynaptic dopamine receptors. The central activity of tetrabenazine relative to its peripheral activity is greater than that of reserpine. It has been found to be useful in the treatment of chorea. The chorea may also be controlled by use of reserpine. Reserpine depletes cerebral dopamine by preventing intraneuronal storage; it is introduced in low doses (e.g., 0.25 mg daily) and daily dose is then built up gradually (e.g., by 0.25 mg every week) until benefit occurs or adverse effects in become troublesome.
Antidepressants: Depression can be treated effectively with standard antidepressants like fluoxetine that is effective treatment for both the depression and the irritability manifest in symptomatic Huntington’s disease. Carbamazepine was found to be effective for depression. Several recent reports suggest that Olanzapine may also be helpful; the dose varies with the patient but 10 mg daily is often sufficient although doses as 30 mg daily are sometimes required. Some other antidepressants including sertraline and nortriptyline can also help to control depression and the obsessive-compulsive rituals that sometimes develop in Huntington’s disease. Lesser potential for abuse and paradoxical excitation. Clozapine was also found to be effective. Carbamazepine was found to be effective for depression. Several recent reports suggest that Olanzapine may also be helpful; the dose varies with the patient but 10 mg daily is often sufficient although doses as 30 mg daily are sometimes required. Some other antidepressants including sertraline and nortriptyline can also help to control depression and the obsessive-compulsive rituals that some people with Huntington’s disease develop. Medications such as lithium can also help to control extreme emotions and swings.

Tranquilizers and Antipsychotic Drugs: Tranquilizers as well as chlorpromazine, haloperidol and imipramine help control chorea movements but they can’t stop metal deterioration. They also alleviate discomfort and depression, making the patient easier to manage. Antipsychotic drugs such as haloperidol and clozapine can help control movements, violent outbursts and hallucinations. Psychosis can be treated with atypical neuroleptics clozapine (50 to 600 mg/day), quetiapine (100 to 600 mg/day) and risperidone (2 to 8 mg/day). These medications control dyskinesias as well as traditional neuroleptics but have fewer extra pyramidal side effects. However, tranquilizers increase patient rigidity. Paranoia, delusional states and psychosis usually require treatment with antipsychotic drugs but doses required often are lower than those usually used in primary psychiatric disorder. In individuals with predominantly rigid Huntington’s disease, clozapine or carbamazepine may be more effective treatment of paranoia and psychosis. Haloperidol is started in a small dose, e.g., 1 mg twice daily and increased every 4 days depending on the response. If haloperidol is not helpful, treatment with increasing of perphenazine up to a total of about 20 mg daily. In some instances, antipsychotic drugs may cause side effects that mimic the signs of Parkinson’s disease including involuntary twitching in the face and body.

Anxiolytic Benzodiazepines: Many patients of Huntington’s disease exhibit worsening of involuntary movements because of anxiety or stress. In these situations, judicious use of sedative or anxiolytic benzodiazepines can be very helpful. Benzodiazepines may also be useful in alleviating aggressiveness or anxiety, but attention must be paid to unsteady gait, sedation and predisposition to aspiration while patients are taking these agents. Long-acting benzodiazepines are favored over short-acting ones because of the lesser potential for abuse and paradoxical excitation. Clomipramine and selective serotonin reuptake inhibitors may be beneficial in controlling obsessive-compulsive behavior associated with Huntington’s disease, as is the case with other dementias.

Anticonvulsants: Individuals with Huntington’s disease occasionally develop myoclonus and seizures that can be controlled effectively with standard anticonvulsant drugs like clonazepam, valproic acid, or other anticonvulsants.

Antibiotics: Antibiotic may treat Huntington’s disease. A common antibiotic holds promise as a treatment for Huntington’s disease, a hereditary disorder for which there is no effective treatment or cure. In mice genetically engineered to develop a similar illness, minocycline, an antibiotic used to treat some forms of acne and arthritis, slowed down the development of symptoms and death from the disease, researchers report. An enzyme called caspase-1 and a substance called nitric oxide are believed to be involved in Huntington’s disease. Since the antibiotic minocycline targets this enzyme and another one involved in the release of nitric oxide, the researchers tested its effects in mice with a disease similar to Huntington’s. Assuming that the drug does slow down Huntington’s disease, it will probably be used in combination with other drugs that are developed to treat the disease.

Miscellaneous: No treatment is available to reverse, retard, or stop the relentless progression of Huntington’s disease. However, several medications, including baclofen, idebenone and vitamin E, have been studied in clinical trials with limited Samples [22]. Some clinical studies have involved using stem cells (the most basic form of cells from which others develop) to grow cells that can be transplanted into the brain of a person affected by the disease. This approach may eventually improve the outlook for those who possess the faulty Huntingtin gene. To control chorea movements without rigidity, choline may be prescribed. A newer treatment for dystonia that is currently given in selected patients is injection of botulinum antitoxin directly into the affected muscle. Institutionalization is usually necessary because of deterioration. Electroconvulsive therapy has been used for patients with severe depression associated with Huntington’s disease. Although drug therapy for
inappropriate sexual behavior is generally reserved as a last option, medroxyprogesterone may be useful. Scientific investigations using electronic and other technologies enable scientists to see what the defective gene does to various structures in the brain and how it affects the body’s chemistry and metabolism. Laboratory animals are being bred in the hope of duplicating the clinical features of Huntington’s disease so that researchers can learn more about the symptoms and progression of Huntington’s disease. Investigators are implanting fetal tissue in rodents and nonhuman primates with the hope of understanding, restoring, or replacing functions typically lost by neuronal degeneration in individuals with Huntington’s disease. Related areas of investigation include excitotoxicity (over stimulation of cells by natural chemicals found in the brain), defective energy metabolism (a defect in the mitochondria), oxidative stress (normal metabolic activity in the brain that produces toxic compounds called here radicals) and tropic factors (natural chemical substances found in the human body that may protect against cell death).

[B] Mental Health Care: The depression rate among people with Huntington’s disease is very high and can be caused by the disease or the challenges it creates. The higher risk for suicide than in the general population and should be openly assessed.

[C] Other Therapies: Huntington’s disease can impair speech, affecting ability to express complex thoughts. Speech therapy can help patients had better retain communication abilities and specialists in swallowing can help prevent choking. Physical therapy can help improve strength, gait and decrease the frequency or seriousness of falls.

[D] Family Support: Family members of people with Huntington’s disease will also need help in coping with the stresses of the disease. Legal and social aid, home care services, recreation and work centers, group housing and institutional care are outside resources patients and their families may need to consider. The general health needs of a person with Huntington’s disease are also important. Dieticians can advise on adequate calorie and nutrient intake. Social and psychiatric support can help with family relationships and antisocial behavior. Family therapy and genetic counseling are often useful for alleviating family conflict and stressors related to relationship losses. Behavioral treatment is likewise a useful strategy for minimizing social isolation and lack of social stimulation. In addition to its neurological and behavioral challenges, the care of patients with Huntington’s disease is often complicated in the extended care setting by the emergence of multiple family issues.

The emotional burden of Huntington’s disease is significant for the spouse, children and other family members. By the time a patient with Huntington’s disease reaches the extended care setting, the family usually emotionally and physically exhausted. Although some family members may feel relieved that they are no longer responsible for the direct care of the patient at home, some may also feel guilty of abandoning their loved ones to the extended care setting. To be able work effectively with the family of a patient with Huntington’s disease, clinicians should be mindful of their own-often complex-emotions. Withdrawal from the patient or over involvement in the patient care is not uncommon. Clinicians should be sensitive to the family’s need to make sense of their loved one’s pathological behaviors and their general expectation that clinicians will provide simple medical explanations for the patient’s symptoms. As with any dementing disorder, careful listening is the first step in working with family members of patients with Huntington’s disease. Clinicians may have to work with hostile and dissatisfied relatives who in turn negatively affect the patient’s behavior. Special attention must be paid to the children of patients with Huntington’s disease. Some may have significant difficulty accepting not only their parent’s diagnosis but also the genetic risk they themselves carry. Genetic counseling should be offered and questions should be answered directly and clearly.

CONCLUSION

It may be concluded that Huntington’s disease is neurodegenerative disorder characterized by midlife onset, involuntary movements, cognitive decline and behavioral disturbances. It is a progressive, autosomal and inherited disorder of the central nervous system characterized by widespread degenerative changes of the cerebral cortex and basal ganglia and other brain regions and the development of prominent chorea and dementia. Genetically, there is no way to predict this disease prior to its occurrence. Although the disease’s progression cannot be stopped or reversed, therapies and support can partially alleviate symptoms and improve quality of life. Treatments include medication, mental health care and speed, swallowing and physical therapies. Symptomatic treatments of Huntington’s disease include use of Dopamine antagonists, Presynaptic dopamine
depleters, Antidepressants, Tranquilizers, Anxiolytic Benzodiazepines, Anticonvulsants and Antibiotics. Several medications including baclofen, idebenone and vitamin E have been studied in clinical trials with limited samples. More research work and clinical trials should be done to search effective drug molecules that would provide a more rational approach in the treatment of Huntington’s disease. The more research should be aimed to develop therapeutic agents that alter the course of neurodegenerative disease like Huntington’s disease by preventing neuronal death or stimulating neuronal recovery. The goal of current research is to develop treatments that can prevent, retard or reverse neuronal cell death. More specific treatments for Huntington’s disease should become feasible with advances in knowledge of their etiology.

REFERENCES