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A Devastating Inherited Neurodegenerative Disease: Huntington's Disease: A Clinical Review

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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 disease occurs in all racial groups but is most common in people of northern European origin. Although no therapy is currently available to delay the onset of symptoms or prevent the progression of the disease, symptomatic treatment of patients with Huntington disease (HD) may improve the quality of life and prevent complications. As is the case with other neurological diseases, HD makes individuals more vulnerable to side effects from medications, particularly cognitive adverse effects. Symptomatic treatment for HD can be divided into drugs to treat the movement disorder and drugs to treat psychiatric or behavioral problems. 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.

Key words: Huntington's disease, Chorea, Neurodegenerative, Brain

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1. Introduction

The disease was originally named Huntington's chorea after George Huntington, who wrote the first detailed description in 1872. More recently, however, the name has changed to Huntington's disease to reflect the fact that chorea is not the only important manifestation of the disease. Many non-motor symptoms may be more disabling and distressing than the motor symptoms. One study assessed the effect of cognitive and motor symptoms on the ability of 67 people with early Huntington's disease to carry out activities of daily living, and found that cognitive impairment was associated with reduced functional ability independent of motor impairment [1, 2].

Huntington's disease is a devastating inherited neurodegenerative disease characterized by progressive motor, cognitive, and psychiatric symptoms. Patients may present with any of these symptoms, and familiarity with the phenotype is therefore important. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes before this [3, 4].

The mean age of onset of symptoms is 40 years, but juvenile onset (<20 years) and older onset (>70 years) forms are well recognized. The Huntington's disease Association (HDA) has records of 6161 adults with symptomatic Huntington's disease and 541 children with juvenile Huntington's disease [2, 5].

Huntington's disease is characterized by prominent neuronal loss in the caudate/putamen of the brain. 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 [3, 5, 6].

Common Symptoms of Huntington's Disease

1. Motor symptoms: Chorea, dystonia, loss of postural reflexes, bradykinesia, rigidity.
2. Psychiatric: Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hyper sexuality (uncommon), psychosis (uncommon)
3. Metabolic: Weight loss, sleep disturbance.
4. Cognitive symptoms: Disorganization as a result of difficulties with planning, initiating, and organizing thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information.
5. Others: Dysphasia (combination of motor and language difficulties), dysphagia (combination of motor problems, impulsivity, and distractibility) [7, 8].

Diagnosis:

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 [9, 10].

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 [11, 12].

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 [9, 13].

Treatment And Management of Huntington's Disease

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[14, 15]. Treatment consists of drug prescription and non-medication advice. Surgical treatment does not play an important role in HD and will be addressed only briefly.

2. Motor signs

Hyperkinesia, or chorea, is treated with dopamine receptor blocking or depleting agents. Most commonly used drugs for chorea (Table 1) are typical or atypical neuroleptics (dopamine receptor blocking) and tetrabenazine (dopamine depleting). The drugs prescribed differ per country. An extensive review of all medication is given by Bonelli. The most commonly used drugs for depression and aggression are listed in Table 2. Clozapine and olanzapine are atypical neuroleptics. Both have an antichoreatic effect. Clozapine requires white cell control in the blood and is, therefore, less practical, making olanzapine the preferred drug. The most frequently reported side effects are weight increase and anti-depressive effects. From small case studies some support can be found for prescribing quetiapine, zotepine, ziprasidone, and risperidon. However, only tetrabenazine, a dopamine depleting drug, has been shown in a controlled trial to significantly reduce chorea [16, 17].

The most common side-effects are depression and sedation. There is a long list of drugs without or with only a very limited result, mostly in open case studies: a-tocopherol amantadine, baclofen, cannabidiol, chlordiazepoxide, choline, clonazepam, creatine, deanol, dextromethorphan, fluoxetine, idebenone, ketamine, lamotrigine, levatiracetam, milacemide, minocycline, muscimol, OPC 14117, PUFA, remacemide, riluzole. Drug treatment for hypokinesia has been tried using antiparkinsonian drugs, but almost always with very disappointing results. In practice, therefore, dopaminergic drug are not prescribed. To date, despite several claims, no drug is available with any neuroprotective or disease-delaying effect. Disease modifying drugs are developed, but not available. Also embryonic cell implants, still under study, are not proven treatment options at the moment. Surgical intervention to treat chorea has been described in a few cases. Deep brain stimulation has a place in other movement disorders such as Parkinson disease. In Alzheimer's disease, anticholinesterase drugs are in use. In Huntington's disease no clinical trials with Rivastigmine or Donepezil are available. In short-term, open studies, no effect was found [18, 19].

Table 1. Drug Treatment for Chorea

Drug	Maximum Dose
Tetrabenazine	200 mg
Olanzapine	20 mg
Tiapride	600 mg
Fluphenazine	10 mg
Pimozide	6 mg
Risperidone	16 mg

Table 2. Drug Treatment for Depression (A) And Aggression (B)

A. Depression		B. Aggression	
Drug	**Maximum Dose**	**Drug**	**Maximum Dose**
Fluoxetine	60 mg	Olanzapine	20 mg
Citalopram	60 mg	Citalopram	60 mg
Mirtazapine	45 mg	Sertraline	200 mg
Carbamazepine	1600 mg	Haloperidol	10 mg
Valproinezuur	2000 mg	Dipiperon	360 mg

3. Psychiatric signs

As depression and aggressive behavior are the most devastating to family life, the majority of drugs are prescribed for these signs. All advice is based on open studies and expert opinion. (Table 2) Besides medication, many other care measures are available. It is important to find the right therapy for the right person at the right time. Non-medical interventions available are: physiotherapy, occupational therapy, speech therapy, dietician, psychologist, social worker, and nurse. During the course of the disease, the patient requires more care, which can also help

his/her partner, for example by having a nurse at home to help with showering. The burden for the caregiver can become too heavy and so help must be found in day-care institutions, usually connected to nursing home facilities. In the period that follows the patient moves into a transition phase and eventually a 24-hour care situation. Throughout the whole process of increasing dependency, psychological help is often needed for the caregiver, who has to deal with increasing responsibilities while losing contact with his or her former partner[19, 20].

Partner groups can be very useful. In general, lay organizations play an enormous role in educating caregivers, patients and families. Medical and non-medical treatment must be individually tailored, as the symptoms and signs differ by person and over time tremendously. Ideally treatment of patients and their families should be organised by a multidisciplinary team. Treatment is intended to improve quality of life. To date, no cure is available unfortunately[21].

4. References

1. Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. Brain Res Rev, **2008,** 58: 209-25.
2. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol, **1985**, 44: 559-77.
3. Rothlind JC, Bylsma FW, Peyser C, Folstein SE, Brandt J. Cognitive and motor correlates of everyday functioning in early Huntington's disease. J Nerv Ment Dis, **1993**, 181: 194-9.
4. Walker FO. Huntington's disease. Lancet, **2007**, 369: 218-28.
5. Nance MA. Comprehensive care in Huntington's disease: a physician's perspective. Brain Res Bull, **2007**, 72: 175-8.
6. Craufurd D, Tyler A. Predictive testing for Huntington's disease: protocol of the UK Huntington's Prediction Consortium. J Med Genet, **1992**, 29: 915-8.
7. Robert MF. Antibiotic Minocycline May Treat Huntington's Disease **2000**. Nature Medicine, 6: 797-801.
8. Phillips W, Shannon KM, Barker RA. The current clinical management of Huntington's disease. Mov Disord, **2008**, 23: 1491-504.
9. Adam OR, Jankovic J. Symptomatic treatment of Huntington disease. Neurotherapeutics 2008; 5: 181-97.
10. Harper PS. The Epidemiology of Huntington's Disease. Hum Genet, **1992**, 89: 365-376.
11. Wild EJ, Tabrizi SJ: Huntington's disease phenocopy syndromes. Curr Opin Neurol, **2007**, 20: 681-7.
12. Rubinsztein DC: Lessons from animal models of Huntington's disease. Trends Genet, **2002**, 18: 202-9.
13. Huntington Study Group: Unified Huntington's disease Rating Scale: reliability and consistency. Mov Disorders, **1996**, 11: 136-42.
14. Henley SM, Wild EJ, Hobbs NZ, Frost C, MacManus DG, Barker RA, Fox NC, Tabrizi SJ: Whole-brain atrophy as a measure of progression in premanifest and early Huntington's disease. Mov Disord, **2009**, 24: 932-6.
15. Vonsattel JP: Huntington disease models and human neuropathology: similarities and differences. Acta Neuropathol, **2008**, 115: 55-69.
16. Shoulson I, Fahn S: Huntington disease: clinical care and evaluation. Neurology, **1979**, 29: 1-3.
17. Huntington Study Group: Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology, **2006**, 66: 366-72.
18. Bonelli RM, Hofmann P: A systematic review of the treatment studies in Huntington's disease since 1990. Expert Opin Pharmacother, **2007**, 8: 141-53.
19. Bonelli RM, Wenning GK: Pharmacological management of Huntington's disease: an evidence-based review. Curr Pharm Des, **2006**, 12: 2701-20.
20. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY: A polymorphic DNA marker genetically linked to Huntington's disease. Nature, **1983**, 306: 234-8.
21. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Philippe K, Demyttenaere K, Dom R, Vandenberghe W, Fryns JP: The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. Eur J Hum Genet, **2007**, 15: 453-62.
22. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's chorea: Guidelines for the molecular genetics predictive test in Huntington's disease. Neurology, **1994**, 44: 1533-6.