

Case Report

Huntington's Chorea a Case Report and Review of Literature

M AFZAL A IQBAL N AZAM K JAVED G SHAHID

Department of Medicine, Naval Hospital (PNS Hafeez), Islamabad

Correspondence to Dr. Muhammad Afzal, Surg. Captain

Key Words: Huntington's chorea, HC, Huntington's disease, HD, Huntington disease.

Huntington's chorea (HC) also known as Huntington's disease (HD), is a rare, progressive and fatal autosomal dominant neurodegenerative disorder, typical of adult onset^{1,2,3}. Involuntary movements, cognitive decline and behavioral disorders leading to functional disability characterize it^{1,3,4}. Huntington's chorea is a complex disease, which does not fit neatly into either physical or psychiatric service provision⁵. HC is encountered throughout the world and found in all ethnic groups³. Its prevalence is 5.15 cases per 100,000 persons and is diagnosed in equal numbers in males and females³. Although the mean age at onset is about 40 years, onset varies from 5–79 years⁶. The gene for Huntington's chorea was identified in 1993 as being a CAG repeat expansion in exon 1 of a gene now known as huntingtin on chromosome 4^{1,7,8}. There is a strong family history of the disease and it is not unusual for more than one family members to be affected^{5,9}. The discovery of the genetic etiology of HC has led to the development of increasing reliable and valid diagnostic tests that can be applied to symptomatic patients, individuals at risk for HC but currently asymptomatic, fetuses and embryos¹. Careful counseling and follow up care are essential if asymptomatic family members are to be tested. Genetic education for general practitioners and physicians is needed, with attention to non-directiveness and the characteristic psychosocial and ethical implications of this particular type of genetic testing.

Case report

A 45 years old gentleman presented to Medical Clinic of Naval Hospital (PNS Hafeez) Islamabad in January 2001 with choreiform movements of the body and early dementia of six months duration. He had a strong family history of similar disease, which included his father and two brothers. On neurological examination he had choreoathetoid movements and features of early dementia. His chest was clinically clear and examination of heart and abdomen was normal. Eye examination did not reveal any evidence of Kayser-Fleischer rings (seen in Wilson's disease). Laboratory investigations showed haemoglobin 13.8 Gm/dl, WBC 7.7 x10⁹/L, serum urea 32 mg/dl, serum sodium 139 mmol/L serum potassium 3.8 mmol/L, ASO titre less than 200 IU/ml, serum bilirubin 6 umol/L, ALT 102 U/L, serum alkaline phosphatase 155 U/L, serum caeruloplasmin 42 mg/dl and serum copper 164 mmol/L (WNL). X-ray chest was normal and CT scan brain

showed early generalized cerebral atrophy. He was managed with haloperidol (0.5mg) 12 hourly, Procyclidine (kemadrin, 5mg) 8 hourly and Propranolol (Inderal 10mg) 8 hourly. He was discharged from hospital with relative improvement after 2 weeks.

Discussion

Although Huntington's disease has existed since at least the seventeenth century, and several physicians provided earlier descriptions of hereditary chorea. It was not generally recognized until the classic description by George Huntington (1850-1916) in 1872¹⁰. HC is a hereditary disorder leading to personality changes, uncontrollable movements, cognitive impairment and ultimately death in mostly adults^{3,11,12,13,14}. It is inherited as an autosomal dominant disorder with complete penetrance. The genetic defect as a CAG trinucleotide repeat expansion at the 5' end of the IT-15 gene on the short arm of chromosome 4⁶. The trinucleotide sequence cytosine – adenine - guanine codes for the amino acid glutamine and the abnormal expansion causes excess glutamine residues to be inserted into protein, leading to the formation of insoluble proteinaceous aggregates^{8, 15}. Such proteins are normally restricted to the cell's cytoplasm. In Huntington's chorea, the aggregates invade the neuron's nucleus, inducing death⁸. The identification of the mutant gene in 1993 paved the way for a decade of basic research^{2,7}. Huntington's chorea transcends the boundaries of race, sex and ethnic background and can be passed from one generation to the next by either the mother or the father. This means that each child of a parent with HC has a 50/50 risk of having inherited the gene, which causes HC.

HC is encountered throughout the world, however, localized geographic clusters of disease exist. Its prevalence is 5.15 cases per 100,000 persons³. This currently affects 30,000 Americans with 150,000 more at risk^{3,13}. Countries that have been settled by Western Europeans have an incidence of the disease similar to the incidence in the United States. The mean age of onset is about 40 years, (5-79 years)⁶. By the time of diagnosis, many patients already have had children and have passed the gene to another generation.

Early Symptoms may appear as slight physical, cognitive or emotional changes^{1,9,12}. The pathognomonic feature is the movement disorder, chorea appears as facial twitching or as twitching and writhing of the distal extremities. Fast eye movements often are impaired. As

HC progresses, the movement disorder becomes more generalized. Eventually the patient's gait is impaired. Rigidity and dystonia predominate in later stages of the disease in adults. In Juvenile cases, rigidity and dystonia may appear as the initial symptom⁴. Symptoms become worse with anxiety or stress. In addition to the initial physical symptoms, there are often very subtle cognitive signs as well. They may involve little more than a reduced ability to cope effectively with new situations. There may be loss of short term memory. Work activities may become more time consuming. Decision making and attention to details may be impaired. Making choices that involve more than two items becomes very stressful¹². Early emotional symptoms may be equally subtle. There may be an accentuation of certain aspects of the individuals normal make up such as more periods of depression, apathy, irritability and impulsiveness or there may be a change in personality. Rarely, a person may become delusional or unrealistically paranoid.

The symptoms of HC most frequently appear between the ages of 30 and 45 with some as young as infants (though rare)¹⁴. Death usually occurs fifteen to twenty years after onset of the disease^{13,14}. The person dies, not from the disease itself but from complications such as pneumonia, heart failure or infection developing from the weakened condition of the body.

HD is a disease of basal ganglia, the portions most severely effected are caudate and putamen. The most significant neuropathological change is a preferential loss of medium spiny neurons in the neostriatum. Biochemically there is marked loss of GABA, substance P, enkephalin and angio-tension converting enzyme¹⁵. Neuronal changes begin very early in life, perhaps even from birth. There is no known treatment that will stop progression^{16,17} but there are symptomatic treatments such as haloperidal, which may control abnormal movements and behavioral disturbances¹⁵. The depression, which is so common in many patients usually, responds to tricyclic anti-depressants or serotonin reuptake inhibitors. It is extremely important for people with HC to maintain physical fitness as much as possible, as individuals who exercise & keep active tend to do better than those who do not. Huntington's chorea can be diagnosed on CT Scan / MRI by caudate atrophy with appropriate history and also by genetic testing¹⁵. Differential diagnosis includes hepatocerebral degeneration, Schizophrenia with tardive dyskinesia, other chorea's and drug reactions^{15,16,17}.

At this time, there is no way to stop or reverse the course of HC. Now that the HC gene has been located, investigations are continuing to study the HD gene with an eye towards understanding how it caused disease in the human body¹⁸. The rapidity of recent discoveries bodes well for further significant progress in understanding and hopefully treating this profoundly debilitating neurodegenerative disorder.

Conclusion

Huntington's chorea is an autosomal dominant progressive neurodegenerative disorder characterized by uncontrolled movements, loss of intellectual faculties, and emotional disturbances. No curative treatment is available and it results in gradually increasing disability. Characterization of the genetic abnormality has dramatically increased our understanding of the underlying mechanisms of the disease process. This is forming the basis of advanced work into the diagnosis, pathophysiology and potential treatment of the disease. Clinically, the availability of genetic testing has eased confirmation of diagnosis in symptomatic individuals. Presymptomatic testing allows at risk individuals to make informed choices but requires supportive care from physicians. Current clinical treatment is focused on symptom control. Advances in research have resulted in the development of potential neuroprotective strategies, which are undergoing clinical testing.

References

1. Russell L. Margolis¹, Christopher A. Ross. Diagnosis of Huntington Disease. *Clinical Chemistry* 2003; 49: 1726-1732.
2. Hogarth P. Huntington's disease: a decade beyond gene discovery. *Curr Neurol Neurosci Rep.* 2003 Jul;3(4):279-84.
3. Harper PS, ed: The epidemiology of Huntington's disease. In: *Huntington's Disease: Major Problems in Neurology*; Vol 31. 2nd ed. Harcourt Brace & Co; 1996:201-39.
4. Vargas AP, Carod-Artal FJ, Bomfim D, Vazquez-Cabrera C, Dantas-Barbosa C. Unusual early-onset Huntingtons disease. *J Child Neurol.* 2003 Jun;18(6):429-32.
5. McGarva K. Huntington's disease: seldom seen--seldom heard? *Health Bull (Edinb).* 2001 Sep;59(5):306-8.
6. Akbas F, Erginel-Unaltuna N. DNA testing for Huntington disease in the Turkish population. *Eur Neurol.* 2003;50(1):20-4.
7. Rosser AE, Dunnett SB. Neural transplantation in patients with Huntington's disease. *CNS Drugs.* 2003;17(12):853-67.
8. Deborah Josefson Molecular basis underlying Huntington's chorea found. *BMJ* 1997;315:445-448.
9. Harper PS, Shaw D: Huntington's disease: genetic and molecular studies. In: Harper PS, ed. *Huntington's Disease: Major Problems in Neurology.* Vol 31. 2nd ed. Harcourt Brace & Co; 1996:241-92.
10. Lanska DJ. George Huntington (1850-1916) and hereditary chorea. *J Hist Neurosci.* 2000 Apr;9(1):76-89.
11. Brouwer-Dudokde Wit AC, Savenije A, Zoetewij MW, Maat-Kievit A, Tibben A. A hereditary disorder in the family and the family life cycle: Huntington disease as a paradigm. *Fam Process.* 2002 Winter;41(4):677-92.
12. Barquero-Jimenez MS, Gomez-Tortosa E. Cognitive disorders in patients with Huntington's disease. *Rev Neurol.* 2001 Jun 1-15;32(11):1067-71.
13. Naarding P, Kremer HP, Zitman FG. Huntington's disease: a review of the literature on prevalence and treatment of neuropsychiatric phenomena. *Eur Psychiatry.* 2001 Dec; 16(8):439-45.
14. Penny JB, Young AB, Huntington's Disease IN Parkinson's Disease and Movement Disorders (eds. Jankovic and Tolosa), 1993, Williams & Wilkins.

Huntington's Chorea

15. Sapp et al. Huntingtin localization in brains of normal and huntington's disease patients. *Ann Neurol* 1997;42:604-12
16. Tyler A, Scourfield J, Morris M: Management and therapy of Huntington's disease. In: Harper PS, ed. *Huntington's Disease: Major Problems in Neurology*. Vol 31. 2nd ed. Harcourt Brace & Co; 1996:161-99.
17. Hersch SM, Greenamyre JT: Huntington's disease. In: *Current Therapy in Neurology*. 1997: 275-79.
18. SuttonBrown M, Suchowersky O. Clinical and research advances in Huntington's disease. *Can J Neurol Sci*. 2003 Mar;30 Suppl 1:S45-52.