ISSN: 2690-909X

Review Article

Advances in Neurology and Neuroscience

Mode of Presentations Anticipation and Penetrance: A Case Series of Huntington's Disease

Towhida Sultana Sumaiya* and Sahariar Hossain Siddik

Dhaka Medical College Hospital, Dhaka, Bangladesh

***Corresponding Author**
Towhida Sultana Sumaiya, Dhaka Medical College Hospital, Dhaka, Bangladesh.

Submitted: 2025, Jul 14; **Accepted:** 2025, Aug 18; **Published:** 2025, Aug 21

Citation: Sumaiya, T, S., Siddik, S, H. (2025). Mode of Presentations, Anticipation and Penetrance: A Case Series of Huntington's Disease. *Adv Neur Neur Sci, 8*(2), 01-03.

Abstract

Huntington's disease (HD) is an inherited, potentially incurable neurodegenerative disease. It typically presents as a triad of progressive psychiatric, cognitive, and motor symptoms, and shows significant anticipation and penetrance. It is due to trinucleotide CAG (cytosine, adenine, guanine) repeat expansion in the Huntington (HTT) gene. It exhibits significant anticipation — earlier onset in successive generations within a pedigree that is due to the instability of the HTT gene, along with a further increase in its length in subsequent generations. Huntington disease reduced penetrance alleles occur at high frequency in the general population. The threshold for disease is 35, with complete penetrance above 39 and incomplete penetrance for 36, 37, and 38 repeats. A series of three cases of HD have been discussed here, along with their pattern of presentation, anticipation, and genetic variation.

Keywords: Huntington's Disease, Penetrance, Anticipation, Genetic Variation

1. Introduction

Huntington's disease (HD) is a chronic neurodegenerative disorder, characterized by the triad of clinical hallmarks: chorea, cognitive impairment, and behavioural disorders [1,2]. Usually, the disease symptoms first appear around the age of 40, but in 5–10% of cases, they manifest before the age of 20 [3].

It is due to trinucleotide CAG (cytosine, adenine, guanine) repeat expansion in the Huntington (HTT) gene. The resulting HTT protein causes dysfunction and death of neurons, with a full penetrance of HD resulting from more than 40 CAG repeats, and a partial penetrance can be seen between 36 and 39 CAG repeats [4]. It shows significant anticipation that is due to the instability of the HTT gene, along with a further increase in its length in subsequent generations. Anticipation simply means the severity of illness in the affected child is greater than that of the affected parent [4]. Characteristic features may also be seen on magnetic resonance imaging (MRI). There is no curative treatment available for HD, and management relies upon symptomatic and supportive measures [5].

Considering the unpredictability of age at onset, variability of clinical features, and of clinical prognosis in HD and the many possible genetic and clinical scenarios associated with the potentially diverse inherited pre-mutational and mutational conditions, accurate knowledge about HD and its genetic aspect must be appreciated. Here, we aim to report on three cases with several generations affected to shape the idea of the mode of presentation, anticipation, and penetrance in HD with available data.

2. Case 1: A 24-year-old man came to us with abnormal behaviour and forgetfulness. Later, he developed choreiform movement of limbs and was diagnosed as a case of Huntington's disease by genetic analysis, where 51 CAG repeats in the allele of the HTT gene were found. In his family, his paternal grandmother and paternal uncle both showed abnormal movement of limbs and forgetfulness at the age of 35 years and 28 years, respectively. They remained undiagnosed and died at an early age. This family clearly showed anticipation.

3. Case 2: A 54-year-old man came to the movement disorder outpatient department with a disabling tremor and abnormal movements of his limbs. With these symptoms, he also had aggressive behaviour and dementia. So, genetic analysis was done on clinical suspicion, and he was diagnosed as a case of Huntington disease, and a 44 CAG repeat was found in the allele of the HTT gene. In his family, both his elder brother and sister had the same type of symptoms but died before a diagnosis. Now his 2 nephews are suffering from Huntington's disease. The patient died a few days ago. In this family, all members showed symptoms after the age of 35. Anticipation is not evident.

4. Case 3: In this scenario, 2 brothers visited our outpatient department with the same set of symptoms. Both of them were presenting with abnormal movements of limbs but no dementia or psychotic symptoms. On a detailed history taking, we found out that their mother died with this type of symptom. Among the 6 siblings, all have features of Huntington disease except the eldest one. This family showed clear anticipation as the younger ones were affected at an early age and have a full triad of symptoms. None of their children were affected till now. We've done their genetic analysis, which came back as 45 CAG repeats in the allele of the HTT gene.

5. Discussion: Huntington's disease (HD) is an inherited, potentially incurable neurodegenerative disease. It typically presents as a triad of progressive psychiatric, cognitive, and motor symptoms, as well as shows significant anticipation and penetrance.

6. Mode of Presentation: In the prodrome of Huntington disease (HD), people may experience mild alterations in their personality, motor abilities, and cognitive abilities. Before the clinical onset of manifest HD, these modest changes may start to appear as early as 15 to 20 years [6-8].

The average age of onset for HD is around 45 years [1]. Approximately two-thirds of those affected first develop neurologic symptoms, while others have psychological problems. In the early stages after diagnosis, symptoms include brief changes in eye movements, coordination, slight involuntary movements, difficulties planning, and a depressed or irritated mood. Affected people are usually able to complete the majority of their normal activities and continue working [1,2].

About 25% of HD patients experience delayed onset till after the age of 50, and some do so until the age of 70. These people experience chorea, dysphagia, and abnormalities in gait, but their symptoms are more prolonged and benign than those of a typical individual [1,7].

In the next stage, chorea becomes more noticeable, voluntary action becomes increasingly difficult, and dysarthria and dysphagia worsen. Most people are compelled to give up their jobs and rely more on others for assistance, while they can still maintain a significant level of personal independence. The impairment is frequently significant, with occasional outbreaks of aggressive behavior and social disinhibition.

In the late stages of HD, motor impairment becomes severe, and the individual is frequently completely reliant, mute, and incontinent. The median survival period from onset is 15 to 18 years (range: 5 to >25 years). The average age of death is 54 to 55 years [1].

7. Penetrance

Alleles containing 36–39 CAG repeats are thought to cause HD. However, their penetrance is not full. People with CAG repeats in this range who are elderly and asymptomatic are not uncommon [9]. More than 95% of alleles have the common [(CAG)n-CAA-CAG] interrupted repeat, which increases disease risk, while only 1% of alleles have the rare [(CAG)n] uninterrupted repeat [10-12]. The deletion of the CAA repeat, also known as the loss of interruption (LOI) variant, will help people with 36–39 CAG repeats alter their risk of developing a disease. Alleles are fully penetrant if they have more than 40 CAG repeats. There have been no reports of old people who are asymptomatic and have alleles of more than 40 CAG repeats [11,12].

8. Anticipation

HD is known to cause anticipation, a phenomenon in which subsequent generations show either a decreasing age of onset or an increasing severity of the disease. When the mutant gene is passed down through the father, anticipation happens far more frequently. The CAG repeat's instability during spermatogenesis is the cause of the anticipatory phenomenon [13]. Paternal transmission is nearly the only way that large expansions (i.e., an increase in allele size of >7 CAG repeats) occur. Although they can occasionally inherit it from their mothers, children with juvenile-onset illness typically receive the enlarged allele from their fathers [14].

Reference

1. Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. Nat Rev Dis Primers 2015; 1:15005.
2. MacDonald, M. E., Ambrose, C. M., Duyao, M. P., Myers, R. H., Lin, C., Srinidhi, L., ... & Harper, P. S. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell, 72*(6), 971-983.
3. Roos, R. A. (2010). Huntington's disease: a clinical review. *Orphanet journal of rare diseases, 5*(1), 40.
4. Stoker, T. B., Mason, S. L., Greenland, J. C., Holden, S. T., Santini, H., & Barker, R. A. (2022). Huntington's disease: diagnosis and management. *Practical neurology, 22*(1), 32-41.
5. Ridley, R. M., Frith, C. D., Crow, T. J., & Conneally, P. M. (1988). Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *Journal of medical genetics, 25*(9), 589-595.
6. Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., ... & Langbehn, D. R. (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *The Lancet Neurology, 12*(7), 637-649.
7. Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., ... & Tabrizi, S. J. (2014). Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology, 10*(4), 204-216.
8. Liu, D., Long, J. D., Zhang, Y., Raymond, L. A., Marder, K., Rosser, A., ... & PREDICT-HD Investigators and Coordinators of the Huntington Study Group. (2015). Motor onset and diagnosis in Huntington disease using the diagnostic

confidence level. *Journal of neurology, 262*(12), 2691-2698.
9. Kay, C., Collins, J. A., Miedzybrodzka, Z., Madore, S. J., Gordon, E. S., Gerry, N., ... & Hayden, M. R. (2016). Huntington disease reduced penetrance alleles occur at high frequency in the general population. *Neurology, 87*(3), 282-288.
10. Ciosi, M., Maxwell, A., Cumming, S. A., Moss, D. J. H., Alshammari, A. M., Flower, M. D., ... & Monckton, D. G. (2019). A genetic association study of glutamine-encoding DNA sequence structures, somatic CAG expansion, and DNA repair gene variants, with Huntington disease clinical outcomes. *EBioMedicine, 48*, 568-580.
11. Lee, J. M., Correia, K., Loupe, J., Kim, K. H., Barker, D., Hong, E. P., ... & Myers, R. H. (2019). CAG repeat not polyglutamine length determines timing of Huntington's disease onset. *Cell, 178*(4), 887-900.
12. Wright, G. E., Collins, J. A., Kay, C., McDonald, C., Dolzhenko, E., Xia, Q., ... & Hayden, M. R. (2019). Length of uninterrupted CAG, independent of polyglutamine size, results in increased somatic instability, hastening onset of Huntington disease. *The American Journal of Human Genetics, 104*(6), 1116-1126.
13. Semaka, A., Kay, C., Doty, C., Collins, J. A., Bijlsma, E. K., Richards, F., ... & Hayden, M. R. (2013). CAG size-specific risk estimates for intermediate allele repeat instability in Huntington disease. *Journal of Medical Genetics, 50*(10), 696-703.
14. Nahhas, F. A., Garbern, J., Krajewski, K. M., Roa, B. B., & Feldman, G. L. (2005). Juvenile onset Huntington disease resulting from a very large maternal expansion. *American Journal of Medical Genetics Part A, 137*(3), 328-331.