Phenotypic Variability in Huntington's Disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder with an autosomal dominant inheritance pattern. It is characterized by a progressive course of the combination of motor, cognitive, and psychiatric manifestations. It is caused because of expansion of CAG trinucleotide repeat in the huntingtin (HTT) gene encoding the protein HTT on chromosome 4. The exact function of normal HTT protein and the mechanism by which mutant huntingtin (mHTT) gene produces manifestation in HD is still unclear. It has been proposed that the mHTT protein contains abnormal long polyglutamine sequences that result in the formation of HTT protein aggregates, which disrupts normal cell functions and ultimately culminates into neuronal loss and neurodegeneration. Current literature shows an important role in cellular aging and various aging-related genes, inducing the disease-specific phenotypes in HD patients.[1,2]

In this issue of the Annals of Indian Academy of Neurology, authors have described the clinical spectrum of HD in 76 genetically proven patients from Eastern India.[3] In this study, the mean age of presentation was 43.21 (±10.14; range 23–65) years and the variation in the age of presentation correlated strongly with the number of CAG repeats. Recent studies proposed that the age of presentation is also influenced by the sequence variation outside the HTT region. Identification of such candidate genes, which act as a genetic modifier in the pathogenesis of HD, will allow for the development of treatment options that can modulate the disease process and, thus, delay or prevent the symptom onset in the individuals carrying mHTT gene.[4]

Paternal transmission is around three times more common as compared with the maternal transmission and associated with earlier age of onset owing to the higher CAG repeat instability during spermatogenesis. In the above-mentioned study, 18.7% had apparently unaffected parents. This subgroup of HD patients, without a family history, are likely to represent sporadic or de novo mutation, which is now well-known to contribute at least 5–8% of genetically proven HD cases.[5]

The majority of the HD patients present with motor features and most of them follow a biphasic course with initial hyperkinetic movements like chorea or dystonia, which gradually plateaus and later replaced by the Parkinsonian features as the disease progresses. This biphasic course corresponds to the selective vulnerability and initial loss of medium spiny neurons (MSNs) of the indirect pathway, leading to hyperkinetic movements followed by the involvement of the direct pathway resulting in hypokinetic movements. The dopamine D2 receptors have been implicated for the selective involvement of indirect pathway MSNs as they are expressed by indirect but not direct MSNs; however, the exact reason is still not clear.[6]

Chorea, followed by dystonia, is the most common hyperkinetic movement disorder noticed in HD patients. Rarely tics have been reported in HD patients, however, it is difficult to clearly distinguish between chorea and tics because both share common jerky nature.[7] While parkinsonian features like rigidity and bradykinesia appear late in adult HD, these symptoms are quite prominent in Juvenile variety (age at onset below 20 years) of Huntington's disease (JHD) which accounts for <10% of the Huntington's disease cases.[6]

The cognitive disturbance is often present in HD patients many years before the onset of motor symptoms and is mostly characterized by subcortical dysfunction including impaired emotion recognition, cognitive slowing, visuospatial and executive dysfunction. The features of frontal lobe involvement are relatively uncommon in HD patients.

A wide variety of behavioral manifestations including apathy, anxiety, irritability, depression, obsessive-compulsive behavior, and psychosis are commonly observed in HD patients. The low frequency of initial psychiatric symptoms noticed by the authors in the above-mentioned study might be the reflection of the tendency to hide psychiatric symptoms by the patient and family member because of the social stigma attached to it.

The triad of chorea, cognitive and neuropsychiatric disturbance is considered to be the characteristic of HD, but in the absence of HTT gene mutation, one should consider HD phenocopies as alternative diagnosis including Huntington disease like 2 (HDL-2) and dentatorubral pallidoluysian atrophy, spino-cerebellar ataxia (types 2, 3, 12 and 17), neuroacanthocytosis and C9orf72 expansions.

The tetrabenazine and its modified version deutetrabenazine are the only two drugs specifically licensed by the US Food and Drug Administration (FDA) for use in patients with HD for the treatment of chorea. Currently, there is no effective disease modifying therapy available for HD patients, however various clinical trials are going on to investigate therapeutic strategies to arrest the disease in the premanifest stage. The most promising disease-modifying approaches that are under trial include therapies aimed at lowering levels of mHTT by targeting either the DNA or RNA of the mHTT gene using anti-sense oligonucleotides (ASOs), RNA interference (RNAi) or small molecule splicing inhibitors.[8] Even after decades of decoding the genetic basis of HD, several aspects of this disease continued to puzzle researchers.

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