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Review Article

Huntington's disease: A Clinically Perceptive and Suggestive Brief Review

Kirti Rani*, Pragya
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, Sec-125, Noida-201303 (UP), India

***Corresponding author**
Dr. Kirti Rani
Email: kirtisharma2k@rediffmail.com

Abstract: Huntington's disease (HD) is a autosomal inherited progressive neurodegenerative disorder that diagnosed with major clinical features having uncontrolled body movements, emotional distress and loss of cognition. Huntington disease tends to progress with the time more quickly than the adult-onset form and affected individuals with worsen neurodegenerative clinical features. The dysfunction and eventual neuronal damage is diagnosed in certain areas of the brain such as cerebral cortex and striatal part of basal ganglia in HD patients. This disease is non-curable and does not have any effective and definite treatment or medication. The preventive measures and treatment used for HD are quite helpful to manage the symptoms of Huntington's disease. But these cannot prevent the physical, mental and behavioral decline associated with its ill and worsen effects in HD patients. It is very important to know the genetic history of patients at right time with available genetic counseling and molecular assay methods to diagnose the existing symptoms during onset of this disease. Hence, it can be treated and managed well at right time in HD patients with effective neuroprotective and suggestive clinical solutions with palliative care must be used to control the clinical and genetic burden in affected population of any country.
Keywords: Huntington's disease; neurodegenerative disorder; chorea; Huntington protein; HD patients

INTRODUCTION:

Huntington's disease (HD) is non-curable progressive neurodegenerative disorder characterized by irregular muscular co-ordination that lead to cognitive loss, chorea and abnormal psychiatric behavior including obsessive-impulsive thoughts and actions [1]. The HD gene has been localized to the short arm of chromosome 4 by linkage to DNA RFLPs and is located in the 4p16.3 region [2]. It is estimated that one in every 10,000 persons have Huntington's disease and juvenile Huntington's occurs is found to be in approximately 16 percent of all total reported cases [3]. It is estimated that in United Kingdom, more than 5700 people, aged 21 years or more, were found to be reported with HD that has been going to be surprising double between 1990 and 2010 [4]. The HD abnormality is due to an expansion of a polyglutamine (CAG) repeat in exon 1 of the Huntington protein [4, 5]. Reported symptoms are gait disorder, progressive dementia, anxiety, stress, tension, difficulty in swallowing, speech impairment, hallucinations, irritability, moodiness, restlessness, fidgeting, paranoid personality disorder and psychosis [6, 7]. Hence, there is no cure for this disease and a rigorous study is required to be done considering the diagnosis, maintenance and treatment of the disease. For this genetic susceptibility, causes, incidence rates, inheritance pattern of the disease need to be studied to know its ongoing epidemiology, prognosis and diagnosis, treatment, available drugs and related implications.

EPIDEMIOLOGY

Huntington's disease is an autosomal dominant neurodegenerative disorder whose onset usually exist between 35 and 50 years of age with wide prevalence form 0.1 to 10/1,00,000 individuals [8, 9]. It was estimated that in 2010, the prevalence of diagnosed adult with HD was 12.3/1, 00,000 individuals in United Kingdom [4]. Its prevalence in the Caucasian population is estimated to be of 5-10 per 100,000 but in Japan, a much lower prevalence of about one-tenth of prevalence of the Caucasion population has been found [5]. Great geographic differences are found in Asia but however, the overall prevalence of HD in Asian continent is found to be 0.40/100,000 , much lower as compared to Europe, North America and Australia with that of 5.70/1,00,000 individuals [10]. In Taiwan, the average annual incidence rate was estimated at 0.1 and the prevalence at 0.42 per 100,000 persons, based on the National Health Insurance database [11]. The prevalence of HD in the Finnish population is lower (0.5/100,000 in1987) than that of other Caucasian populations, partly explained by the low frequency of HTT haplo-group A among the Finns [12]. Prospective studies on clinically diagnosed cases have yielded a prevalence of 7/100,000 in Australia [13] and a prevalence of 10.6/100,000 in Northern Ireland [14].

Currently, the higher incidence of Huntington's disease in white populations was recorded as compared with African or Asian people that related to the higher frequency of Huntington alleles with 28–35 CAG repeats in white individuals [15].

PATHOLOGY AND CLINICAL FEATURES

HD is characterized by irrepressible motor dysfunction, cognitive decline and psychiatric disturbances, which lead to progressive dementia and death approximately 15–20 years after disease onset [16]. Adult-onset of HD is characterized by a triad of progressive motor, cognitive, and emotional symptoms while in juvenile-onset HD that typically presents with voluntary movement abnormalities, the clinical diagnosis of adult-onset HD is typically made after the onset of involuntary motor abnormalities, primarily chorea and mild chorea, abnormal extra ocular movements, brisk muscle stretch reflexes, and diminished rapid gait alternating movements are the most consistent early findings in manifest disease [17]. Their occurs certain psychiatric symptoms include anxiety, depression, delusions, hallucinations, lack of motivation and suicidal thought along with motor and cognitive symptoms like choreiform movement; stumbling, difficulty in walking; clumsiness, loss of balance/coordination; decreased volitional movement; difficulty eating, speaking and swallowing; memory impairment; decreased concentration; difficulty in planning, organizing and reasoning (executive symptoms) and behavioral changes including irritability and apathy [18]. The HD gene was cloned 11 years ago and since then an explosion of research has led to many insights into the normal function of HTT (Huntington) and the molecular basis of the disease [16]. A mutation in the Huntington (HTT) gene causes an increase in the number of trinucleotide CAG (Cytosine, Adenosine, Guanine) repetitions, always 36 or more for individuals with HD [19]. Variance in the age of onset of the disease has been correlated with the number of CAG repeats and this mutation is collectively known as polyglutamine (polyQ) diseases because the trinucleotide repeat encodes an expanded stretch of glutamines in their corresponding proteins [20]. HTT is a 348-kDa multi-domain protein that contains a polymorphic glutamine/ proline-rich domain at its amino-terminus [16]. In humans, hemizygous loss of one of the two huntington genes has been observed as a result of either a terminal deletion of one chromosome 4 including HD gene in patients with Wolf-Hirsch horn syndrome related polyQ disease spin bulbar muscular atrophy (SBMA), which is caused by a CAG repeat expansion in the androgen receptor which cause progressive weakness and muscle atrophy due to loss of their motor nerve supply and mild androgen insensitivity (MAIS) [21]. Mutant HTT is pathogenic and its accumulation contributes to cell toxicity and reduced viability in Huntington's disease as two major protein degradation pathways, namely ubiquitin–proteasome system and autophagy–lysosome pathway that lead to abnormal interaction between the mutant HTT and autophagic vesicles [22]. It was also reported that ubiquilin proteins involved in facilitation of protein disposal through the proteasome and lysosomal degradation pathways are diminished in Huntington's disease that lead to pathological alteration at single neuronal level and reducing ability of neurons survival [23, 24, 25]. Interactions of HTT with HTT-associated protein 1 (HAP1) was also found that its interactions with HTT-interacting protein 1 (HIP1) are decreased with increased polyglutamine length and it may resulted in an endogenous toxicity mediated by increased intracellular HIP1 [26]. It has been found that HD-associated symptoms are alleviated by inhibition of the kinase mTOR that facilitated the activating interaction between Rheb and mTOR and Striatum-specific deletion of the gene encoding TSC1, an inhibitor of mTOR. This interaction was accelerated the onset of HD phenotypes in mice, consistent with excessive mTOR activity contributing to HD [27]. The mitochondrial calcium defect was also observed in human patients containing an abnormally long polyglutamine repeat that occurred early in HD pathogenesis [28]. Genome-wide expression profiling of human blood has been also reported that is very well known to reveal biomarkers for Huntington's disease [29]. In another study, a transcriptional factor was also isolated from blood has been found to serve as a potential biomarker of the disease [30]. it was found that hyper activation of medial prefrontal regions compensated for reduced sub cortical participation during time discrimination in pre-HD and become early neurobiologic marker of neuronal dysfunction as well as, other designed electrophysiological measures can also might have been serve as potential biomarkers for HD [31, 32].

DIAGNOSIS

Diagnosis of HD plays a very important role before its treatment given to HD patients. Various methods have been used for the diagnosis and testing of HD. Various psychiatric and neurological diagnostic tests are to be done for the diagnosis of HD along with brain imaging by EEG (electroencephalogram) and right genetic counseling to know exact family history for predicting the likeliness of a patient to have HD or the likeliness of him/her to transfer the gene to their next progeny. Molecular diagnosis have been successfully performed by genetic testing in which genomic DNA was isolated from the lymphocytes of the patients and the length of the CAG repeats were assessed by means of polymerase chain reaction (PCR) analysis by using the RS1 and WP2 primers, flanking the CAG repeat [33, 34].

TREATMENT

Striatal degeneration in Huntington's disease (HD) was also noticed that leads to dysfunction of the cerebral cortex affecting striatal part of basal ganglia. Hence, severe neuropsychiatric symptoms are reported

such as mental depression, bradykinesia, dysarthria and muscular irritability or rigidity. These reported symptoms are found to be reported very common and problematic sometimes in most cases of prescribed medication to treat HD patients with limited effectiveness [35, 36]. Sertraline, a selective serotonin reuptake inhibitor, have been used to treat genetically confirmed Huntington's disease in which severe irritability and aggressiveness reported in patient [37]. In certain studies, Nabilone drug has been found to be suitable for HD treatment as it improves both motor and psychiatric symptoms in a patient with HD [36]. In other studies, histone deacetylase inhibition was done with sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype of Huntington's disease mice model [38]. Tetrabenazine (a dopamine-depleting agent) is also reported one of the more effective agents for reducing chorea but it has a risk of potentially serious adverse effects. So, use of neuroleptic agents, such as olanzapine and aripiprazole, may have adequate efficacy with a more favorable adverse effect profile than older neuroleptic agents for treating chorea and psychosis in HD patients [39]. A effective medication was done to treat HD patients called, Neuroprotective Gene Therapy for Huntington's Disease that was used with Polymer-Encapsulated Engineered cell to Secrete Human Ciliary Neurotrophic Factor have found to be safe, feasible and tolerant in phase I trials [40]. CNTF-expressing lentiviral vector in the quinolinic acid rat model of Huntington's disease was shown to have neuroprotective effect making lentiviruses efficient gene delivery system for the screening of therapeutic molecules in Huntington's disease. [41]. Gene silencing therapy and stem cell therapy done by striatal cell transplantation in animals was already used successfully in patients of other neurodegenerative diseases and hence, it can might have potential to treat HD [42]. Treatment of the movement disorder in HD patients is aimed by keeping the experimental portal to restore the balance of neurotransmitters in the basal ganglia and neuroprotective or neurorestorative by neurotransplantation [43]. Several medications were also having been reported earlier including controlled and permissible clinical trials of baclofen and idebenone and vitamin E [44]. HTT protein was also reported ubiquitously expressed in human tissues but the predominance of the interest in the pathology lies if it could might have been positively happen in the central nervous system (CNS) only. Hence, most of the current therapeutics for HD has been targeted to prevent neuronal damage in the CNS and most of the evidences have been accumulated to suggest that the maintenance of a healthy nervous system is tightly linked with peripheral physiological health. Therefore, that can be used in treatment of both the peripheral and central pathophysiologies of HD which could form the basis of a more effective HD therapeutic strategy [45].

CLINICAL IMPLICATIONS

Despite intensive research efforts have been devoted to investigate molecular mechanisms of pathogenesis and effective therapy for this devastating disease. But, no effective and definite ideal model is still not available at present as which become worse with the time to have lethal effects of neuropathology and progressive motor and cognitive impairments in HD patients [46]. Other implication related to this disease is that the risk of attempting suicide to have suicidal behavior of HD patients during the diagnosis and palliative care due to experiencing unwanted psychiatrics argue against ill vision of society and surrounding environment [47].

CONCLUSION

Hence, this review can might have prove helpful to understand getting the effective diagnosis, timely treatment of HD patients and its related clinical implications with adopted palliative care. Especially, most challenging implication is required to be take care of fluctuating mood and physiological ill behavior to attempt suicide by HD patients during tits diagnosis and treatment. Caring for people with HD is very challenging due to lacking of definitive treatments. But careful attention to fluctuating symptoms and good communications of HD patients with physicians, counselor, close relatives, friends and surrounding social environments that can contribute to the successful management of this non-curable disease. The goals of adopted treatments and medication can be helpful to reduce the burden of symptoms, maximize function, and optimize quality of life of HD patients.

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