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A CLINICAL PERSPECTIVE REVIEW ON HUNTINGTON'S DISEASE

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ABSTRACT

A huntingtin gene CAG expansion on chromosome 4 is the source of the severe genetic disorder known as Huntington's disease (HD). This leads to an overly lengthy polyglutamine tract, which is detrimental. While the wild-type huntingtin protein performs vital functions, the mutant form has a number of negative side effects. The etiology of HD involves disruptions in various cellular processes, including autophagy, reduced mitochondrial activity, lysosomal dysfunction, and others. Proper protein folding is hampered by the elongation, which promotes greater HTT protein aggregation and accumulation. HD usually appears in people between the ages of 30 and 50, while longer CAG repeats can cause the start to happen earlier. Dystonia and akinesia arise as a result of the loss of substance-P containing medium spiny neurons in the direct pathway. Epilepsy frequently causes seizures. CAG repetitions typically have lengths greater than 53. The two most widely used are the Coulson and Fahn functional capacity measure and the Unified Huntington Disease Rating measure (UHDRS). Among the pharmacological treatments available are selective serotonin reuptake inhibitors, such venlafaxine and mirtazapine, which have both noradrenergic and serotonergic effects. Psychoactive medications have the potential to reduce violence and psychosis. Promising research is being done on potential disease-modifying therapies, such as ways to increase clearance and decrease mutant huntingtin levels. Ongoing clinical research offers hope for future medicines to HD patients and their families.

INTRODUCTION:

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by uncontrollable choreatic movements alongside cognitive and behavioral impairments. It arises due to the expansion of cytosine, adenine, and guanine (CAG) trinucleotide repeats on chromosome 4p16.3 within the Huntingtin (HTT) gene. This genetic mutation results in an excessively elongated polyglutamine segment within the HTT protein, promoting neurodegeneration. Furthermore, the elongation fosters increased aggregation and accumulation of the HTT protein, hindering proper protein folding. Typically, HD manifests in individuals aged 30 to 50, though the onset may occur earlier with longer CAG repeats[1].

Clinical diagnosis of Huntington's disease (HD) is established in individuals displaying motor, cognitive, or behavioral symptoms, particularly if there's a family history of the condition. Confirmation is typically achieved through DNA testing. For those at risk, pre-symptomatic testing can identify gene carriers. Unfortunately, there's no cure for HD, and patients often rely heavily on caregivers as the disease advances. Treatment focuses on enhancing quality of life and managing complications. Pneumonia and suicide are frequent causes of mortality in HD patients.

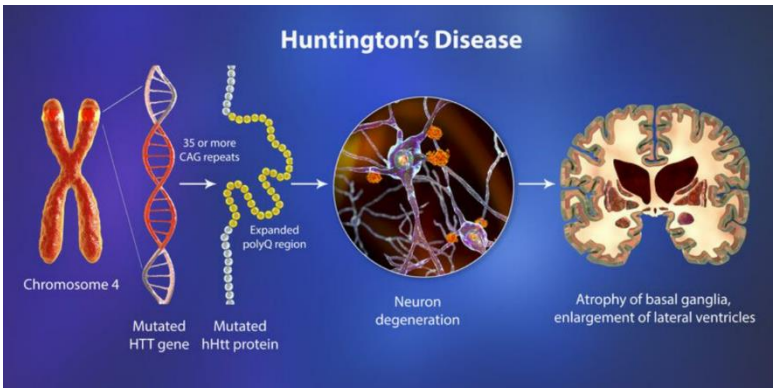

FIG-1. Huntington's disease.

Huntington's disease (HD) arises from an expansion of CAG trinucleotide repeats within the huntingtin gene on chromosome 4, following an autosomal dominant inheritance pattern. This expansion leads to the formation of an abnormal huntingtin protein with an elongated polyglutamine sequence[2]. Disease manifestation is certain with more than 39 CAG repeats, while penetrance is reduced between 36 and 39 repeats. Inheritance from the father's side may increase the likelihood of a child inheriting an expanded pathogenic repeat length, as sperm cells tend to exhibit greater repeat variability and larger repeat sizes compared to other tissues in the body.

Huntington's disease (HD) exhibits varying prevalence rates across different populations. In European communities, the prevalence ranges from 10 to 13 cases per 100,000 individuals, whereas in East Asia, it is considerably lower at 1-7 cases per million. In South Africa, Black populations demonstrate lower rates compared to White and mixed communities. These disparities in HD prevalence are linked to genetic variations within the huntingtin (HTT) gene among different ethnic groups. Typically, communities with higher incidence rates tend to have longer typical CAG repeat lengths.

Pathophysiology of Huntington's Disease.

The hallmark of Huntington's disease (HD) is the progressive degeneration of neurons within the putamen, caudate nucleus, and cerebral cortex.

Particularly, the selective degeneration of enkephalin-containing medium spiny neurons in the basal ganglia's indirect pathway forms the foundation for chorea. Moreover, the loss of substance-P containing medium spiny neurons in the direct pathway contributes to the emergence of dystonia and akinesia. The distinct pattern of neuronal loss in specific regions of the cortex and basal ganglia among affected individually likely contributes to the observed variability in clinical manifestations.

There are multiple theories in the pathogenesis of HD, and more than one process can occur at the same time:

1.Neuronal aggregates: Intracytoplasmic and intranuclear inclusions containing the mutant HTT are components of the proteolytic pathway in HD. Accumulation of these mutant protein aggregates could lead to an impairment of the ubiquitin-proteosome pathway.

2.Transcriptional dysregulation.

3.Excitotoxicity: This is due to a combination of increased glutamate as well as glutamate agonist release from the cortical afferents.

4.Mitochondrial dysfunction and altered energy metabolism.

5.Changes in axonal transport and synaptic dysfunction[3].

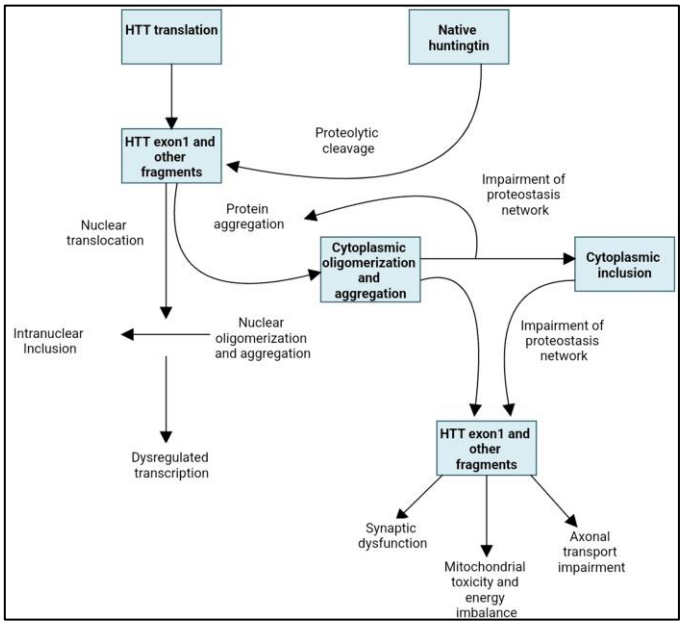

FIG-2. Pathogenic cellular mechanisms of Huntington's Disease.

The mutant huntingtin gene causes dysfunction and neuronal death via several routes. The direct effects on cellular homeostasis, neuronal transport, transcription, translation, mitochondrial function, and synaptic function of the locus one mutant huntingtin (mHTT) segment, as well as the propensity of mHTT to form aberrant aggregates. The negative effects of that are more prone to affect the striatal medium spiny neurons. Pathology related to stroke develops in two stages. A hyperkinetic phenotype is caused by the loss of medium spiny neurons (MSNs) of the indirect pathway in the first phase, while a hypokinetic trait is caused by the loss of medium spiny neurons of the direct path in the second phase. D2 dopamine receptors may be involved because they have been connected to the pathophysiology of huntington's disease and are expressed indirectly, not directly, by MSNs. However, other variables may have also contributed to the indirect pathway of MSNs preferential sensitivity. Reduction of brain-derived neurotrophic components, glutamate excitotoxicity based on corticostriatal estimations, and negative effects of repeat-associated non-ATG translation proteins are more theories[4].

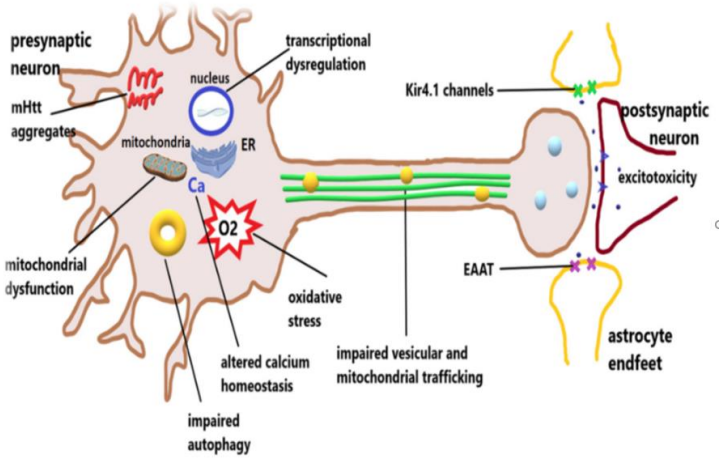

FIG-3. Pathophysiology of Huntington's Disease.

The expression of abnormal, mutant huntingtin (mHtt) makes the protein prone to misfolding and aggregation, leading to impaired proteostasis. Autophagy is also defective in HD, caused by impaired recognition of cargo and vesicular trafficking. Mutant Htt interacts with a series of transcription factors, causing impaired transcription of a series of essential proteins, such as brain-derived neurotrophic factor, or proteins acting as pro- or anti-apoptotic factors. The mitochondrial dysfunction caused by mHtt, together with the altered calcium homeostasis, leads to increased oxidative stress, which further impairs mitochondrial function.

Interaction of mHtt with motor proteins causes altered vesicular (yellow circles) and mitochondrial trafficking along the microtubules to distant sites of the neuron with deficient neuromediator release, especially of inhibitory neuromediators (light blue circles). In addition, deficient astrocytic function caused by the decreased function of inwardly rectifying K^+ channels and diminished clearance of excess glutamate through reduction of excitatory amino acid transporter 2 (EAAT), together with altered function and distribution of N-methyl-D-aspartate receptors (NMDARs, blue arrow heads), creates the premises for excitotoxicity[5].

Clinical narration of Huntington's Disease

Pathognomonic indications and symptoms of Huntington's disease encompass a spectrum of intellectual, musculoskeletal, and psychiatric disturbances. Additional, albeit less recognized, symptoms include unintentional weight loss, disruptions in sleep patterns and circadian rhythms, and dysfunction of the autonomic nervous system. While the onset of Huntington's disease can range from 2 to 80 years, the average age of onset typically falls between 35 and 45 years. The disease tends to endure for approximately 16 to 18 years, progressing to increased reliance on assistance for daily tasks and ultimately resulting in fatality. Lung infections represent the primary cause of death, followed by suicide[30].

Neuromuscular manifestations in Huntington's disease are characterized by involuntary and unwanted movements, which primarily affect minor facial muscles and the distal extremities such as toes and fingers. These muscle spasms are often subtle and may go unnoticed by observers or be misinterpreted as signs of anxiety.

As the disease progresses, a person's gait may become unsteady, resembling drunkenness. These involuntary movements gradually spread to involve other muscle groups, moving from distal to proximal areas of the body.

Choreatic gestures dominate the individual's waking hours, with variations in facial expressions including eyebrow raises, blinking, head movements such as bowing or turning, and protrusion of the tongue with pursed lips. Extension movements of the back muscles become increasingly prominent. Some individuals experience difficulties with speaking and swallowing, leading to a risk of choking, and eventually progressing to muteness. Speech and eating challenges become more pronounced as the disease advances[6].

Individuals affected by Huntington's disease subsequently experience a slowing of movement and difficulty initiating movements. The severity of hypokinesia and chorea varies among individuals, ranging from juvenile patients with pronounced stiffness to elderly patients in advanced stages of the disease who may be bedridden with stiffened limbs and flexion contractures. Sluggish movements and increased muscle tone result in abnormal postures such as torticollis and rotational movements of the trunk or limbs, characteristic of dystonia.

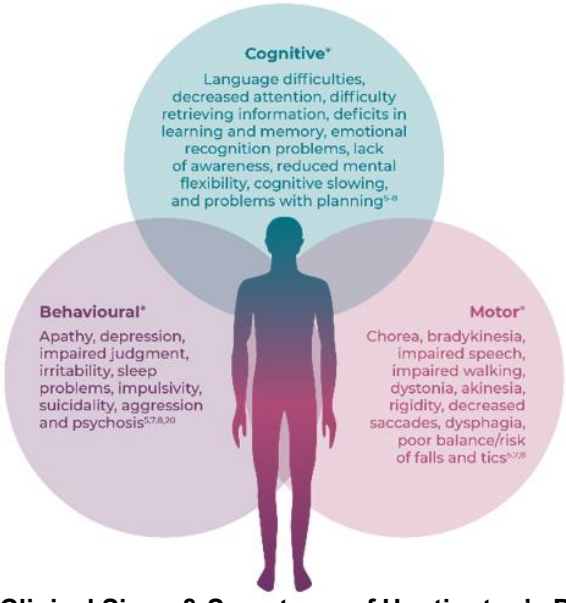

FIG-4. Clinical Signs & Symptoms of Huntington's Disease.

Dystonia may present as the initial motor symptom of Huntington's disease. Tics, although relatively uncommon, are another form of involuntary movement. Cerebellar dysfunction may manifest intermittently, resembling hypo- or hypermetria. Movement difficulties are often likened to intoxication or cerebellar ataxia, making it challenging to differentiate between choreatic and ataxic gait. Pyramidal signs may also be inadvertently present[7].

As time progresses, the neurological impairments increasingly affect the ability to carry out daily activities. Tasks such as getting out of bed, bathing, dressing, using the restroom, household chores, cooking, and eating become progressively more challenging. Motor symptoms eventually impede the efficiency of tasks, regardless of the type of activity the patient engages in, even as psychological and cognitive changes remain prominent[29].

Psychological symptoms often manifest in the early stages of Huntington's disease, often appearing before motor symptoms. Research indicates that anywhere from 30 to 77 percent of patients exhibit these symptoms, significantly impacting the daily lives of families.

The presence of weight loss and apathy further complicates diagnosis. Common emotional experiences include feelings of guilt, fear, and low self-esteem. Apathy, rather than anxiety or depression, is particularly associated with the disease's progression. Individuals in the early symptomatic stage and those who carry the pre-manifest gene are at a higher risk of suicide, especially during periods such as gene testing or when their sense of identity begins to diminish.

Nervousness is also common, occurring in 30-60% of cases, often related to uncertainties surrounding the onset and progression of the disease Obsessive-compulsive disorder (OCD) can significantly disrupt the life of patients, often

Impatience, which may initially appear subtle, can persist throughout all stages of the illness and may manifest in various forms, from heated arguments to physical violence[27].

Apathy, characterized by decreased enthusiasm and increased passive behavior, can be difficult to distinguish from depression. Psychosis typically emerges in the final phase of the disease, often alongside cognitive decline, resembling delusions and auditory hallucinations seen in schizophrenia[8]. Hypersexuality can pose challenges, particularly in the early stages of marriage, but later transitions into hyposexuality

Mental deterioration, a key symptom of Huntington's disease, may precede motor symptoms and can be relatively mild in the early stages before progressing as the disease advances. Executive functions are notably affected by cognitive changes[26].

In Huntington's disease, individuals struggle to prioritize and organize their daily activities in a goal-directed manner, a skill they previously possessed. This leads to difficulties in planning and managing their lives effectively[29]. They become less mentally flexible and find it challenging to adapt their thinking to different situations.

Their responses may no longer align with expectations, hindering problem-solving abilities. While speech remains relatively unaffected, semantic recall may be partially preserved initially but ultimately declines over time. Overall, all cognitive functions experience significant slowing down[9].

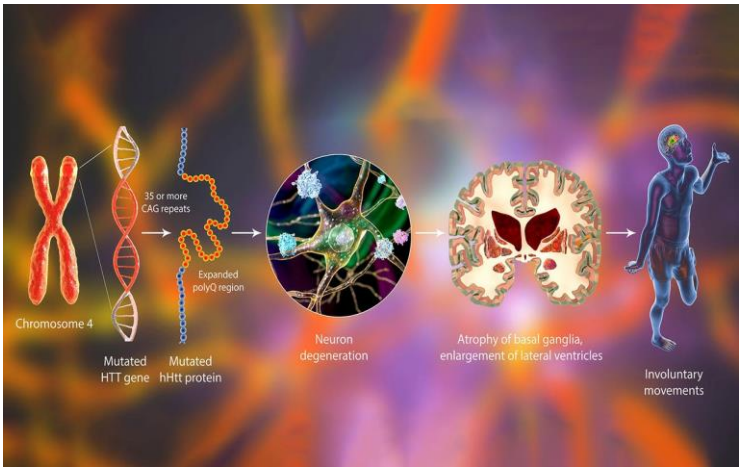

FIG-5. Clinical challenge of Huntington's Disease chorea.

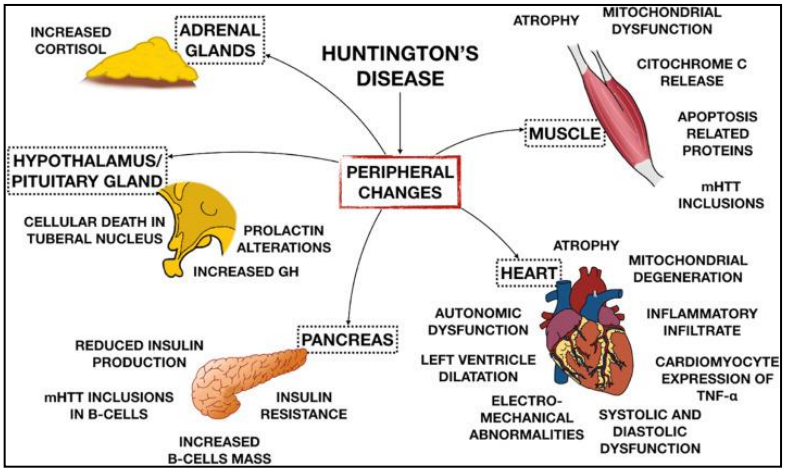

FIG-6. Peripheral Changes of Huntington's Disease.

Unintentional weight loss has become a consistent finding across all individuals affected by Huntington's disease right from the onset. However, with increased awareness of this issue, weight loss seems to be less severe due to its multifaceted nature. Contrary to expectations, research has revealed that neither chorea nor any other movement disorders are directly associated with weight reduction. Instead, there appears to be a correlation between the length of CAG repeats and other contributing factors[28].

Logistical challenges, such as sluggishness, decreased appetite, difficulties in food management, and swallowing issues, undoubtedly contribute to weight loss. Additionally, the destruction of hypothalamic neurons is identified as another contributing factor to this phenomenon.

Sleep disturbances and disruptions to the body's internal clock in Huntington's disease (HD) have only recently garnered attention. Autonomic abnormalities may trigger episodes of excessive sweating in affected individuals. When clinical symptoms first manifest before the age of 20, the condition is termed Juvenile HD, often characterized by social abnormalities and academic struggles[25].

Musculoskeletal involvement commonly displays features of dystonia and reduced movement. Choric movements typically appear in the second decade of life and are less common in the first. Epileptic seizures are frequent occurrences. In most cases, the length of CAG repeats exceeds 53. Notably, in 75% of cases involving affected children, the affected parent is usually the father[10].

Evaluation of Huntington's Disease

Accurate clinical assessment of Huntington's disease manifestations is vital for individuals, families, and caregivers. Various standardized scales have been developed for systematic monitoring, primarily for research purposes. Among the most widely recognized are the Unified Huntington Disease Rating Scale (UHDRS) and the Coulson and Fahn functional capacity scale. Additionally, there are other scales in use, including those assessing quality of life[11]. The European Network for Huntington's Disease (EHDN) has developed a comprehensive set of assessment measures, which are currently utilized by over six thousand patients across Western countries.

Diagnostics

The confirmation of Huntington's disease typically relies on several factors including the commencement of motor impairment as assessed by the Unified Huntington's Disease Rating Scale, total motor score, and diagnostic confidence score. Additionally, a documented family history or a positive genetic test further supports the diagnosis. A score of four on these assessments typically signifies motor onset or the presence of "obvious" Huntington's disease, with scores ranging from zero to four.

However, it's important to note that Huntington's disease also has a premanifest phase, which can be detected up to 11-16 years before the onset of manifest disease. During this phase, individuals may exhibit mild motor, intellectual, and psychological deficits[12].

Differential Diagnosis

A Huntington's phenocopy refers to a condition characterized by the trio of chorea, neurocognitive, and psychiatric symptoms similar to Huntington's disease, but without the presence of the mutated huntingtin (mHTT) gene variant. While several genetic disorders can mimic Huntington's phenocopies, confirmation is only possible in about 2-4% of cases. Among these, the two most prevalent in Western populations are spinocerebellar ataxia 17 and C9orf72[24].

Dentatorubral-pallidoluysian atrophy should be considered, especially in cases involving convulsions. Additionally, neuroferritinopathy and neurodegeneration with brain iron accumulation are two disorders characterized by iron deposition that may present with atypical diagnostic imaging findings[13].

In cases of neuroacanthocytosis, aberrant acanthocytes can be observed on peripheral blood smear. Among the Nigro people, Huntington's disease-like syndrome 2 is the most frequent cause of Huntington's phenocopies, according to studies.

Genetic Guiding

Following the identification of the gene's location on chromosome 4 in early 1983, linking analysis was employed for the first time to enable the identification of individuals in the premanifest stage. Initially, findings from linkage studies were provided to candidates with a confidence level of 93%, which subsequently increased to approximately 98%. A genuine premanifest diagnosis became possible for individuals at risk of Huntington's disease once the CAG repeats on chromosome 4 was identified in early 1993[23]. This breakthrough served as a model for addressing novel concerns and issues, marking the first instance where such a treatment became genuinely feasible[14]. The Huntington society, comprising researchers, medical professionals, and laypeople, subsequently authored a manifesto outlining the accepted practices in this area.

Steps	Guidelines
Step-1	Clinical genetics consultation, ideally in conjunction with a psychiatrist and a neurologist.
Step-2	A second session that includes a blood sample is held four to six weeks later.
Step-3	There will be a session with disclosure following six to eight weeks.

Table 1. Steps of genetic guiding in Huntington's disease.

The protocol was extended to require the candidate to make every effort to obtain a result from the parent with a 50% chance of having Huntington's disease. Subsequently, candidates with a 25% risk can undergo assessment[21].

Prenatal diagnosis

Prenatal detection is achievable as genetic testing can be conducted on any cell containing nuclei with the genetic code. Chorionic villus sampling can be performed between weeks 10-12 of gestation, while amniocentesis and genetic testing can be carried out around weeks 15-17. However, the process only commences if the parents are aware of their own genetic condition, to prevent inadvertent disclosure to both parties simultaneously[15].

If the Huntington gene is identified in the foetus, termination of the pregnancy may be considered, although the parents

cannot be compelled to make this decision. Alternatively, an exclusion test can be conducted by comparing the genetic profile of the foetus with that of the grandparents if the parents' genotypes remain unknown. This test can result in either a 0% risk for the embryo, maintaining the parent's 50% status, or a 50% risk for the embryo, indicating an equal risk to that of the parents. Couples then have the choice to terminate a pregnancy in which the embryo is at a 50% risk[16].

Over the past decade, pre-implantation diagnosis has become available in several countries. This involves genetic analysis of a single cell from an eight-cell stage embryo obtained through assisted reproduction techniques. Embryos lacking the extended CAG repeat are selected for implantation to allow a typical gestation to proceed. However, not all nations adhere to this approach, and it is essential to establish the chromosomal makeup of both parents before initiating this treatment.

Management

Despite the fact that the underlying pathophysiology of Huntington's disease remains unknown and there is currently no known cure, there exist various treatment options aimed at managing the disease's manifestations and symptoms with the objective of enhancing the quality of life. While many symptoms may not necessarily require treatment, interventions are determined based on the patient's functional abilities. There is a lack of comprehensive data regarding the prescription or optimal dosage for managing clinical symptoms, thus pharmacological interventions are customized to the individual and rely on professional judgment[17]. Treatment encompasses both medication therapy and non-pharmacological interventions such as counselling.

Neurocognitive symptoms

Among the symptoms of Huntington's disease, chorea often emerges prominently. Tetrabenazine stands out as the sole medication approved specifically for managing chorea. With daily dosages ranging from 50 to 75 milligrams, this inhibitor of synaptic vesicular amine transport provides sustained antichretic effects.

Common adverse effects include insomnia, anxiety, stress, and restlessness. Deutetrabenazine, a deuterium-containing derivative of tetrabenazine, exhibits a longer half-life and reduced metabolic variability. In the initial Huntington study, deutetrabenazine significantly reduces chorea, particularly when compared to a placebo. Although direct comparisons between tetrabenazine and deutetrabenazine are lacking, evidence suggests that deutetrabenazine may have fewer side effects, such as anxiety and insomnia[18].

In a randomized study, the neuroleptic sulpiride demonstrated effectiveness in managing chorea. Additional neuroleptics like risperidone and quetiapine are also commonly used in clinical practice, albeit their main adverse effects include drowsiness and weight gain.

Physiotherapy is frequently employed to address additional motor symptoms such as abnormal gait, poor balance, and frequent falls. Recommendations for treating psychiatric symptoms in Huntington's disease are primarily based on clinical assessment and professional judgment due to limited data in this area. Non-pharmacological therapies like behavioral therapy or interpersonal psychotherapy may be utilized to address mental health issues such as anxiety, panic disorder, and irritability. However, these approaches may be limited in the presence of cognitive impairments[19].

Pharmacological treatments include selective serotonin reuptake inhibitors like mirtazapine and venlafaxine, which exert serotonergic and noradrenergic effects. Psychoactive medications can be beneficial in managing aggression and psychosis. Various drugs have been explored for treating apathy, although randomized controlled trials are lacking. Surgical interventions play a minor role in the management of Huntington's disease and will be discussed briefly[20].

CONCLUSION:

Over the last two decades, there has been remarkable progress in increasing awareness of Huntington's disease (HD) and improving patient care. The extensive duration spent in the premanifest phase, prior to symptom onset, often goes unnoticed due to the disease's typical course lasting over 17 years. HD not only impacts the individual affected but also profoundly affects their families throughout their lives. There has been a significant proliferation of research articles on HD during this time.

Currently, the focus of research lies primarily on understanding the disease's pathogenesis and identifying biomarkers. Advancements in drug development are anticipated to arise from a deeper understanding of the disease's underlying mechanisms. Efforts are underway to discover medications capable of slowing down, delaying, or halting the onset of the disease.

Another key area of focus is the ongoing pursuit of accurate and easily identifiable indicators signalling the beginning of the disease's terminal phase. The European Huntington Disease Network's database research is a flagship initiative aimed at laying the groundwork for larger investigations once potential medications become available for human trials.

Simultaneously, efforts are being made to provide the best possible care for all HD patients and individuals at risk, while also striving to identify effective treatments for the condition. While the discoveries thus far are promising, it is acknowledged that there is still a considerable distance to cover before finding a definitive solution.

BIBLIOGRAPHY

1. Faysal M, Khan J, Zehravi M, Nath N, Singh LP, Kakkar S, Perusomula R, Khan PA, Nainu F, Asiri M, Khan SL. Neuropharmacological potential of honokiol and its derivatives from Chinese herb Magnolia species: understandings from therapeutic viewpoint. Chinese medicine. 2023 Nov 24;18(1):154.
2. Roos RA. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010 Dec 20;5:40.
3. Finkbeiner S. Huntington's Disease. Cold Spring Harb Perspect Biol. 2011 Jun 01;3(6)
4. Caron NS, Wright GEB, Hayden MR. Huntington Disease. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. University of Washington, Seattle; Seattle (WA): Oct 23, 1998.
5. van Duijn E, Kingma EM, van der Mast RC: Psychopathology in verified Huntington’s disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007, 19:441-8.
6. Wheelock VL, Tempkin T, Marder K, et al.: Predictors of nursing home placement in Huntingtondisease. Neurology. 2003.
7. Kohan ZG: Huntington’s disease, third edition: Oxford monographs on medical genetics. Eur J Hum Genet. 2004.
8. Aziz NA, van der Burg JM, Landwehrmeyer GB, Brundin P, Stijnen T, Roos RA: Weight loss in Huntington disease increases with higher CAG repeat number. Neurology. 2008.
9. Kremer HP, Roos RA, Dingjan GM, et al.: The hypothalamic lateral tuberal nucleus and the characteristics of neuronal loss in Huntington’s disease. Neurosci Lett. 1991,

10. Aziz NA, Swaab DF, Pijl H, Roos RA: Hypothalamic dysfunction and neuroendocrine and metabolic alterations in Huntington's disease: clinical consequences and therapeutic implications. Rev Neurosci. 2007.
11. Arnulf I, Nielsen J, Lohmann E, et al.: Rapid eye movement sleep disturbances in Huntington disease. Arch Neurol. 2008.
12. Arnulf I, Nielsen J, Lohmann E, et al.: Rapid eye movement sleep disturbances in Huntington disease. Arch Neurol. 2008, 65:482-8. 10.1001/archneur.65.4.482
13. Quarrell OW, Nance MA, Nopoulos P, Paulsen JS, Smith JA, Squitieri F: Managing juvenile Huntington's disease. Neurodegener Dis Manag. 2013.
14. Shoulson I, Fahn S: Huntington disease: clinical care and evaluation. Neurology. 1979, 29:1. 10.1212/wnl.29.1.1
15. Huntington Study Group: Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord. 1996, 11:136-42.
16. Huntington Study Group. (2021). Accessed: July 31, 2022.
17. European Huntington’s Disease Network. Accessed: July 31, 2022.
18. Ross CA, Aylward EH, Wild EJ, et al.: Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014, 10:204-16.
19. Wild EJ, Mudanohwo EE, Sweeney MG, et al.: Huntington's disease phenocopies are clinically and genetically heterogeneous. Mov Disord. 2008, 23:716-20.
20. Hensman Moss DJ, Poulter M, Beck J, et al.: C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. Neurology. 2014, 82:292-9.
21. Wild EJ, Tabrizi SJ: Huntington's disease phenocopy syndromes. Curr Opin Neurol. 2007, 20:681-7.
22. Gusella JF, Wexler NS, Conneally PM, et al.: A polymorphic DNA marker genetically linked to Huntington's disease. Nature. 1983, 306:234-8.
23. International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. J Med Genet. 1994, 31:555-9.
24. Maat-Kievit A, Vegter-Van Der Vlis M, Zoeteweij M, et al.: Predictive testing of 25 percent at-risk individuals for Huntington disease (1987-1997).
25. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, et al.: The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. Eur J Hum Genet. 2007, 15:453-62.
26. Huntington Study Group: Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology. 2006, 66:366-72.
27. Coppen EM, Roos RA: Current pharmacological approaches to reduce chorea in Huntington's disease. Drugs. 2017, 77:29-46.
28. Frank S, Testa CM, Stamler D, et al.: Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. JAMA. 2016, 316:40-50.
29. Rodrigues FB, Duarte GS, Costa J, Ferreira JJ, Wild EJ: Tetrabenazine versus deutetrabenazine for Huntington's disease: twins or distant cousins?. Mov Disord Clin Pract. 2017, 4:582-5.
30. Eddy CM, Parkinson EG, Rickards HE: Changes in mental state and behaviour in Huntington’s disease. Lancet Psychiat. 2016, 3:1079-86.

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