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Huntington's Disease

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ABSTRACT

Huntington's disease (HD) is a rare but devastating neurodegenerative disorder. HD is more prevalent in western countries. HD patients suffer from neuropsychiatric, cognitive, and motor symptoms. Uncontrolled and irregular movements called chorea are the characteristic symptom of HD. Neuropsychiatric symptoms occur nearly a decade after motor symptoms are detected. Upon the appearance of early motor symptoms, an evaluation of family history is sufficient for the diagnosis of HD. However, a genetic test is definitive regarding the presence or absence of HD. It is caused by a single mutation in chromosome 4. Healthy people have 35 CAG triplet repeats at the end of a gene called HTT in their genome. This gene codes for a protein called huntingtin. Huntingtin is involved in various functions in the body. HD patients have 36 or more CAG repeats in their genome. When this mutant gene is expressed, it produces mutant huntingtin (mHTT). mHTT breaks down into toxic fragments. Striatum is a part of the brain associated with motor control, decision making, and motivation. It is most affected by the toxicity of mHTT. The number of CAG repeat predicts the onset of symptoms. The greater the number of CAG repeats, the earlier the symptoms will appear. If more than 35 CAG repeats are present in a person's genome, then HD cannot be prevented. There is no disease-modifying treatment for HD. Currently approved drugs only ameliorate chorea in HD. Gene editing has the potential to treat HD at its core. Treatments either help the clearance of mHTT or prevent the HTT gene from expressing. There are drugs in clinical trials that have shown to either slow down the progression or reverse HD in animal models.

INTRODUCTION

HD is a rare, familial, monogenetic, progressive neurodegenerative disorder usually beginning in the prime working years and marked by the progressive development of psychiatric symptoms,

cognitive impairment, and involuntary jerky movements called chorea. HD is one of nine polyglutamine diseases. It was first identified by Dr. George Huntington in 1872 [1]. HD is an inherited autosomal-dominant disorder. It is caused by cytosine-adenine-guanine (CAG) trinucleotide repeat expansion at the 5' end of the huntingtin gene. If the onset of HD symptoms is in childhood, it is called juvenile HD. In the late-onset of HD, symptoms appear in the seventh or eighth decade of life.

EPIDEMIOLOGY

HD is not equally prevalent around the world. HD is more prevalent in the West as compared to Asian countries [1]. This variation is attributed to the difference in length of the HTT gene among different ethnicities [2]. A study using a commercial insurance database in the US found that the prevalence of HD is 6.52 per 100,000 persons and its incidence is 1.22 per 100,000 person-years [3]. Juvenile HD makes up only 5% of total HD cases [4]. The average life expectancy after midlife diagnosis of HD is 15–20 years [4]. The gene responsible for HD is on autosomal chromosome so HD is not gender specific. Males and Females have almost the same risk of getting HD.

SYMPTOMS

HD patients suffer from motor dysfunction, cognitive decline, and neuropsychiatric symptoms. On average the symptoms appear when the patient reaches 40 years [4]. The characteristic symptom of HD is involuntary movements of limbs, face, and neck. Involuntary movements are quick, irregular, unpredictable, and jerky movements of muscles that are not in a person's control. These involuntary movements are known as chorea. Over time, they progress to a severe form called dystonia which is slow, repetitive movements that can disrupt normal posture. Parkinsonian symptoms often accompany chorea in HD. Bradykinesia (slowness) and rigidity (stiffness) are the

forms of parkinsonian symptoms that lead to falls and injuries in the later stages of HD [5]. Muscle impairment in the throat results in difficulty of speech (dysarthria) and difficulty in swallowing (dysphagia) [6]. Choking is quite common in HD patients and the resulting "aspiration pneumonia" is the leading cause of death among HD patients [6,7]. All these motor symptoms can be divided into two broad categories:

1) Involuntary movements include chorea, dystonia, and athetosis.

2) Impairment of voluntary movements which include bradykinesia and apraxia.

Neuropsychiatric symptoms of HD include depression, irritability, apathy, a decline in executive function, obsessive-compulsive behaviors (OCBs), and perseverative behaviors (PBs) [8]. Irritability in medical terms means the tendency to become frustrated easily [9]. OCB is a mental disorder in which a person obsessively experiences certain thoughts or the urge to perform such tasks that create distress. PBs are the continuation and repetition of a response whose stimulus no longer exists. Hallucinations and delusions are common in HD patients [10]. Cognitive decline in HD is categorized as subcortical dementia in which slowness of thoughts is encountered along with memory deficit. Around 40% of HD patients have mild cognitive impairment (MCI) [11]. These psychiatric symptoms are found in 73–98% of HD patients [1]. The negative feelings such as guilt and depression that come with these neuropsychiatric symptoms often give rise to suicidal thoughts. Suicide can be the third leading cause of death in HD [12].

All these symptoms do not start at the same time, rather their onset can differ by a decade. In the pre-symptomatic stages of the disease, involuntary movements are subtle and unnoticeable. Neuropsychiatric symptoms appear about 11 years before the onset of motor impairment [8]. HD patients also suffer from weight loss, cardiac failure, and skeletal muscle atrophy [13]. If left untreated, the severity of these symptoms increases with time. In the later stages of the disease, motor impairment, cognitive disability, and neuropsychiatric symptoms can be so severe that

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performing daily life activities becomes impossible and the patient needs round-the-clock caregiving. Nonpsychiatric symptoms are more difficult for caretakers to deal with as compared to motor symptoms. This dependence and disability ultimately lead to death.

DIAGNOSIS

Diagnosis of HD is much simpler in comparison to other neurodegenerative disorders such as Alzheimer's disease. Diagnosis of HD does not involve biomarkers and magnetic resonance imaging (MRI). However, biomarkers and MRI are used to rule out the possibility of other neurodegenerative disorders particularly if family history is not available. Biomarkers are also used to determine the prognosis of the disease and to evaluate the effectiveness of treatment [14].

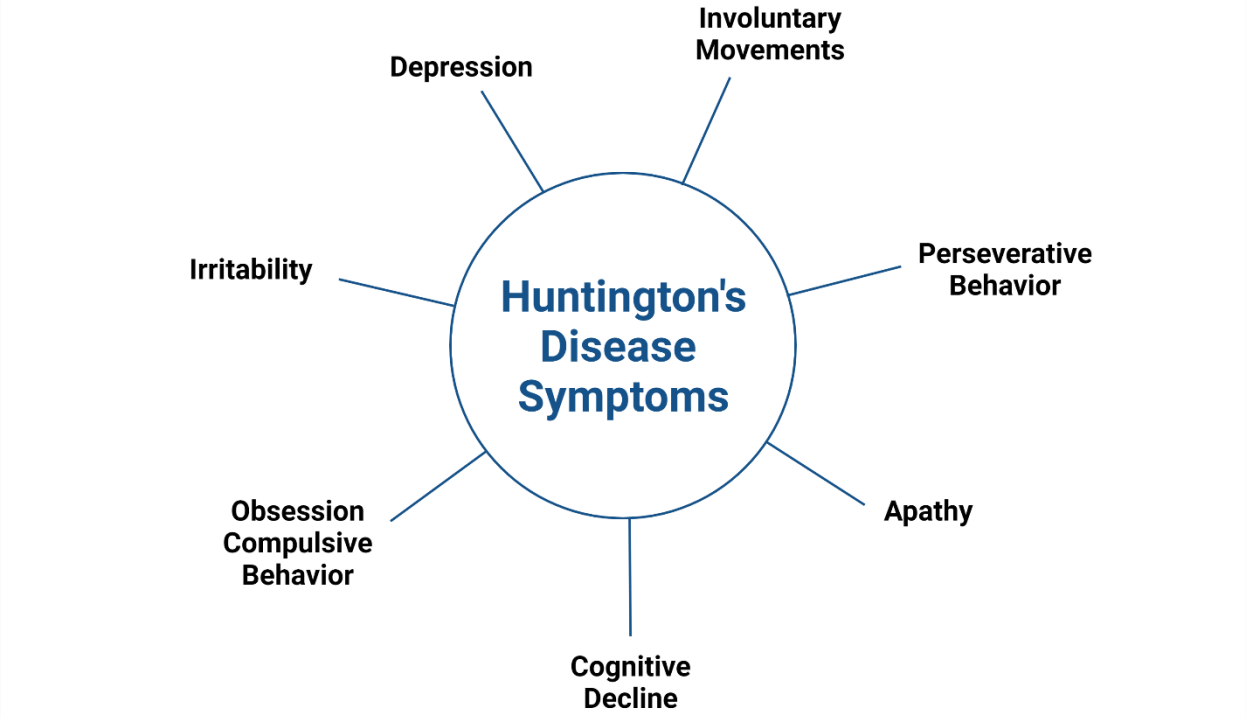

Figure 1. Major symptoms of HD

Diagnosis of HD can be based on one or more of the following three factors:

1) Family history

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2) The onset of motor symptoms

3) Genetic testing

In clinical setting, the first sign of HD can be subtle motor symptoms. In the presence of motor symptoms, family history is evaluated. Finally, genetic testing affords an unambiguous indication of the presence of HD based on the CAG repeat length in a person's genome [15]. If one parent of a person had HD, there is a 50% chance of that person developing HD [16]. In addition, genetic testing can predict whether a person is going to incur HD decades before the onset of even the subtle motor symptoms. Motor symptoms are evaluated using a score between 0 to 4 [2]. Unified HD Rating Scale (UHDRS) and the Problem Behaviors Assessment (PBA) are the commonly used rating scales to evaluate the frequency and severity of symptoms in HD patients [11].

Only about 1% of total patients who are thought to have HD are misdiagnosed [15]. These patients have HD-like symptoms but genetic testing does not show abnormal CAG repeat in them. This condition is known as HD phenocopy. HD phenocopy shows similar motor and neuropsychiatric symptoms but they are due to different underlying pathophysiology. The most common HD phenocopies are frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). HD is divided into 5 stages (Table: 1).

Stage of HD	Description
1. Early Stage:	Early-stage begins when HD is diagnosed. The person in the early stage of HD is able to perform everyday tasks. It lasts for about 8 years.
2. Early intermediate stage:	This is the stage where HD patient begins to face difficulties in everyday task. The patient may carry on these tasks but his/her efficiency of doing these tasks is decreased. Chorea

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	begins to appear in this stage. It can last from 3 to 13 years.
3. Late intermediate stage:	This is the stage where the patient becomes disabled. Motor and neuropsychiatric symptoms worsen with time. It can last from 5 to 16 years.
4. Early advanced stage:	HD patient becomes dependent on 24/7 care. At this stage of the disease, there is no hope that the patient will ever be able to take any financial or domestic responsibility. The distress of family members and caregivers increases with every passing day. This stage can range from 9 to 21 years of onset of HD.
5. Advanced stage:	This is the stage where parkinsonian symptoms appear. Patients suffer from difficulties in speech and swallowing. Death occurs mostly due to aspiration pneumonia, but sometimes due to heart failure and infection.

Table 1: Five stages of HD [17–20]. *Symptoms worsen as disease progresses into advanced stages.*

PATHOPHYSIOLOGY

Huntingtin is a normal protein found in our body. The gene that encodes huntingtin is located on chromosome number 4. The healthy gene for huntingtin also called wild type HTT, has 9 to 35 repeating units of CAG sequence [21]. People suffering from HD have a mutation in their HTT gene due to which it has more than 35 CAG repeats. HD becomes fully penetrant when the CAG repeat exceeds 39 [22]. This mutation does not occur inside an individual, rather it is inherited from a parent. The number of CAG repeats is related to the penetrance of HD and the timing of onset of symptoms. CAG repeat is not the only factor responsible for symptoms and progression

of HD. Environmental and behavioral factors also influence the progression of the disease. This is evident by the fact that identical twins suffering from HD show differences in their clinical profile of the disease. In healthy human beings not suffering from HD, huntingtin protein encoded by wild-type HTT is scattered throughout the body having different functions in early embryonic development, neurogenesis, as a scaffolding protein, regulation of transcription, and synaptic connectivity [13,23]. Mutant HTT gene having more than 35 CAG repeats codes an abnormal protein called mHTT, which has additional glutamine residues due to extra CAG repeats. In the case of HD, there is a gain of function in the polyglutamine part of mHTT and a loss of function in the normal part of mHTT. The toxic effects of mHTT are due to polyglutamine. Neurodegeneration in HD is due to loss of function in the normal part of mHTT. Aggregates of mHTT are found in the nucleus, cytoplasm, and neural processes of the neurons in the brain. The presence of these aggregates in the different parts of the brain seems to indicate the timing of the onset of HD. In adult-onset of HD, these aggregates are in the cytoplasm of the neurons while in Juvenile HD, they are in the nucleus. This mHTT is cleaved within the neurons to form toxic fragments. The toxic effects of these fragments include disruption of transcription and post-transcriptional processes, abnormalities of synaptic plasticity, disruption of neuronal transport, and inhibiting the release of brain-derived neurotrophic factor (BDNF) that are required for the survival of neurons. Medium spiny neurons (MSNs) located in the striatum of the brain are particularly devastated by the toxic effects of mHTT aggregates [22]. Neurons in striatum die due to excessive stimulations called excitotoxicity, through glutamate stimulation of N-Methyl-D-aspartic acid (NMDA) receptors. Gamma-aminobutyric acid (GABA) and opioid receptors in the striatum are decreased [24]. Dopaminergic, glutamatergic, and GABAergic signaling are also affected in HD. Dopamine is a neurotransmitter (messenger between the neurons) in the brain that is associated with movements and feelings of motivation and reward. Chorea in HD is due to overstimulation

caused by an increased level of dopamine in the brain [10]. That's why the drugs that block the dopaminergic pathway are effective in treating chorea in HD.

On the macroscopic level, HD causes a shrinkage in the brain size through neurodegeneration in the caudate nucleus and putamen parts of the striatum (Figure 2) [25,26]. Other parts of the brain

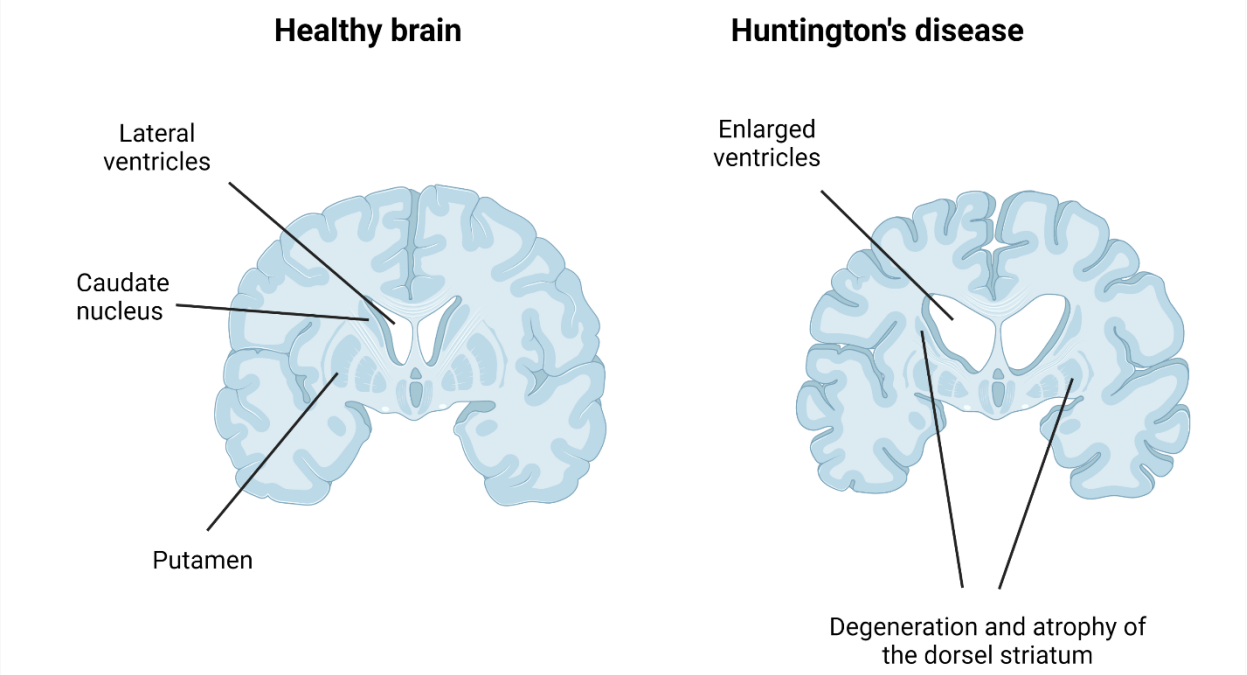

Figure 2. Brain of HD patients shrinks due to neurodegeneration in the striatum

affected by HD include cortical ribbon. In advanced stages of the disease, other parts of the brain such as basal ganglia and cortical are also affected [27]. Neurodegeneration starts from the posterior cortical region and proceeds to the anterior cortical as the disease progresses. White matter changes in HD result in loss of connectivity in the brain.

RISK FACTORS

GENETICS

HTT is the gene responsible for HD. It is an autosomal dominant gene that shows high penetrance [28]. CAG expansion length is the strongest risk factor for developing HD, which generally occurs in individuals with ≥36 repeats. Greater numbers of repeats are associated with earlier age of onset and may potentially influence clinical progression.

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AGE

For the people having a CAG triplet repeat in their genome, the risk of HD increases with age. However, age is not a deterministic factor. The onset of symptoms depends upon the length of the CAG repeat. The greater the number of CAG repeats, the earlier the symptoms will appear. If the number of CAG repeat is over 60, then HD symptoms appear before adulthood. This is called juvenile HD [1].

PREVENTION

Unfortunately, HD cannot be prevented. People having more than 35 CAG triplet repeats in their genome will inevitably get HD. The symptoms of HD can be managed through proper treatment.

TREATMENT

HD is one of the best-studied and understood neurological diseases but there is still no disease-modifying treatment for it. All of the currently available drugs only manage the symptoms of HD. Drugs approved by the US Food and Drug Association (FDA) do not reverse or stop the progression of HD, they manage the symptoms by targeting Dopaminergic signaling pathways.

CHOREA TREATMENT IN HD

Chorea in HD is caused by abnormal levels of dopamine in the brain. Drugs that act on the dopaminergic pathway to balance its level in the brain can be effective against chorea.

Tetrabenazine

Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor. VMAT2 is an important enzyme in the dopaminergic pathway. It packs dopamine into vesicles so that it can be secreted in the synaptic cleft (microscopic space between two synapses) [29]. The blockage of VMAT2 causes dopamine to degrade prematurely [30]. Tetrabenazine is approved by FDA for the treatment of chorea in HD. Tetrabenazine was introduced in the 1970s, it selectively binds to VMAT2 reducing their activity, thus reducing dopamine levels in the brain [29]. A drop in dopamine level reduces chorea.

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Deutetrabenazine

Deutetrabenazine is approved by FDA for the treatment of chorea in HD [31,32]. It is also a VMAT2 inhibitor. Deutetrabenazine also reduces the amount of dopamine released into the synaptic cleft by blocking VMAT2 [31]. Interestingly, this drug is a deuterated (replacing six hydrogen with six deuterium) form of tetrabenazine.

CLEARANCE OF MHTT

mHTT is cleared from the cell through its degradation through macroautophagy. Drugs that enhance this natural process can be beneficial in HD.

Rapamycin

Mammalian target of rapamycin complex 1 (mTORC1) decreases the autophagy of mHTT. Rapamycin can inhibit mTORC1 thus facilitating the autophagy of mHTT [33]. Due to decreased levels of mHTT, its toxic effects on cells are also decreased. Another drug called felodipine can induce autophagy using an mTOR-independent pathway. Rapamycin and felodipine were found effective in mice models of HD [33].

Autophagosome-tethering compound

Autophagosome-tethering compound (ATTEC) facilitates autophagy of mHTT by binding to mHTT and autophagosome [33]. They do not interact with healthy huntingtin protein in the body and can pass through the blood-brain-barrier (BBB) easily. By lowering mHTT, ATTEC eliminates the toxicity in the cells.

Selisistat

Selisistat reduces the levels of mHTT in the cell through autophagy by inhibiting silent information regulator T1(SirT1) [34]. Selisistat produced encouraging results in Drosophila (a fruit fly) models of HD but the initial stages of its clinical trials have been disappointing.

REDUCING THE EXPRESSION OF THE HTT GENE

These techniques stop the expression of the mutant gene responsible for HD. HD is caused by a single gene, so there is an opportunity to treat HD by stopping that gene from expressing itself into mutant protein.

CRISPR/Cas9

DNA targeting can either affect the transcription of HTT or directly edit the gene itself. Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated system (Cas) can precisely cut DNA at specified sequences. Gene editing using

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CRISPR/Cas9 is shown to reduce mHTT in mice models of HD [35,36]. Although this technology cannot eliminate all the mHTT, it still has the potential to mitigate some of the devastating symptoms of HD. There is a risk of mutations in the CRISPR-Cas9 method [37].

Antisense oligonucleotides

Once the mutant HTT gene is transcribed to mRNA, antisense oligonucleotides (ASO) can either degrade it or prevent it from translating into mHTT [33,34]. By doing so ASO can prevent the formation of mHTT and its toxic fragments. Tominersen previously known as IONIS-HTTRx by Roche pharmaceutics is one such ASO drug that aims to treat HD [38,39]. It is in clinical trials. ASOs cannot cross BBB, so they have to be injected directly into the brain.

microRNA

microRNA can be delivered selectively into striatum using appropriate vectors. microRNA inhibits the expression of the HTT gene [33]. Preclinical studies using this technique have produced encouraging results and this method is under clinical trials.

Zinc-finger nucleases

Zinc-finger nucleases (ZFN) are a class of proteins that can affect the transcription of DNA. Using ZFPs, it is possible to repress the transcription of the gene responsible for HD. ZFPs are delivered through Adeno associated virus (AAV) [37]. ZFPs were shown to reduce the production of mHTT in mice models of HD [34].

SYNAPTIC MODULATION

Memantine

Memantine is an NMDA receptor antagonist that is usually used to treat some of the symptoms of Alzheimer's Disease. It reduces the harmful effects of glutamate in the brain. Memantine has the potential to ameliorate chorea in HD [34].

Pridopidine

Pridopidine is a Sigma-1 Receptor (S1R) agonist. S1R is involved in neurogenesis and synaptic plasticity [40]. It also reduces oxidative stress. S1R dysfunction is related to numerous neurodegenerative diseases. Pridopidine has produced disease-modifying effects in animal models of HD but it did not show significant positive results in its early human studies [40]. Pridopidine is still in clinical trials.

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CONCLUSION AND FUTURE PROSPECTS

HD provides an opportunity to study the course of a neurodegenerative disease decades before the onset of even the most subtle symptoms. Genome-wide association study (GWAS) has made it possible to study the genetic basis of HD. Despite this, there is no disease-modifying treatment for HD. Gene editing poses an opportunity to cure HD at its core. ZFN's can repress the expression of HTT while CRISPR/Cas9 has the potential to eliminate defective genes responsible for HD from a person's genome. Treatments for HD should target multiple targets at once. It may be possible that CRISPR/Cas9 and immunotherapy can be used in combination to treat HD. CRISPER/Cas9 can eliminate mHTT from inside the cells while immunotherapy can eliminate mHTT from the extracellular environment. In this way, their cumulative effect can be beneficial in the treatment of HD. DNA and RNA-based approaches to treat HD should be further developed. Molecular therapies against mHTT expression are in early development. Newly emerging technology will pave the way for the development of novel treatments for HD and its delivery into the brain. Treatments for HD produce good results in preclinical studies but they do not slow the progression or reverse HD in clinical trials. More efforts are required to ensure a reliable treatment for this rare but devastating disease.

REFERENCES

1. Goh, A.M. *et al.* 'Huntington's disease: Neuropsychiatric manifestations of Huntington's disease'. *Australas Psychiatry*. (2018) 26(4), 366–375. DOI: 10.1177/1039856218791036.
2. McColgan, P. *et al.* 'Huntington's disease: a clinical review'. *Eur J Neurol*. (2018) 25(1), 24–34. DOI: 10.1111/ene.13413.
3. Bruzelius, E. *et al.* 'Huntington's disease in the United States: Variation by demographic and socioeconomic factors'. *Mov Disord*. (2019) 34(6), 858–865. DOI: 10.1002/mds.27653.
4. Snowden, J.S. 'The Neuropsychology of Huntington's Disease'. *Arch Clin Neuropsychol*. (2017) 32(7), 876–887. DOI: 10.1093/arclin/acx086.
5. Reilmann, R. 'Parkinsonism in Huntington's disease'. *Int Rev Neurobiol*. (2019) 149, 299–306. DOI: 10.1016/bs.irn.2019.10.006.
6. Pizzorni, N. *et al.* 'Management of dysphagia in Huntington's disease: a descriptive review'. *Neurol Sci*. (2020) 41(6), 1405–1417. DOI: 10.1007/s10072-020-04265-0.
7. Heemskerk, A.-W. *et al.* 'Dysphagia in Huntington's Disease: A Review'. *Dysphagia*. (2011) 26(1), 62–66. DOI: 10.1007/s00455-010-9302-4.
8. Oosterloo, M. *et al.* 'Obsessive-Compulsive and Perseverative Behaviors in Huntington's Disease'. *J Huntingtons Dis*. (2019) 8(1), 1–7. DOI: 10.3233/JHD-180335.
9. Karagas, N.E. *et al.* 'Irritability in Huntington's Disease'. *J Huntingtons Dis*. (2020) 9(2), 107–113. DOI: 10.3233/JHD-200397.
10. Loi, S.M. *et al.* 'Huntington's disease: Managing neuropsychiatric symptoms in Huntington's disease'. *Australas Psychiatry*. (2018) 26(4), 376–380. DOI: 10.1177/1039856218766120.
11. Petersén, Å. *et al.* 'The psychopharmacology of Huntington disease'. *Handb Clin Neurol*. (2019) 165, 179–189. DOI: 10.1016/B978-0-444-64012-3.00010-1.
12. Kachian, Z.R. *et al.* 'Suicidal ideation and behavior in Huntington's disease: Systematic review and recommendations'. *J Affect Disord*. (2019) 250, 319–329. DOI: 10.1016/j.jad.2019.03.043.
13. Jimenez-Sanchez, M. *et al.* 'Huntington's Disease: Mechanisms of Pathogenesis and Therapeutic Strategies'. *Cold Spring Harb Perspect Med*. (2017) 7(7). DOI: 10.1101/cshperspect.a024240.

14. Przybyl, L. *et al.* 'What, When and How to Measure-Peripheral Biomarkers in Therapy of Huntington's Disease'. *Int J Mol Sci*. (2021) 22(4). DOI: 10.3390/ijms22041561.

15. Ghosh, R. *et al.* 'Clinical Features of Huntington's Disease'. *Adv Exp Med Biol*. (2018) 1049, 1–28. DOI: 10.1007/978-3-319-71779-1_1.

16. Smedley, R.M. *et al.* 'Genetic testing for Huntington's disease: A thematic analysis of online support community messages'. *J Health Psychol*. (2021) 26(4), 580–594. DOI: 10.1177/1359105319826340.

17. Saldert, C. *et al.* 'Comprehension of complex discourse in different stages of Huntington's disease'. *International Journal of Language & Communication Disorders*. (2010) 45(6), 656–669. DOI: 10.3109/13682820903494742.

18. Paulsen, J.S. *et al.* 'Depression and Stages of Huntington's Disease'. *JNP*. (2005) 17(4), 496–502. DOI: 10.1176/jnp.17.4.496.

19. Novak, M.J.U. *et al.* 'Huntington's disease: clinical presentation and treatment'. *Int Rev Neurobiol*. (2011) 98, 297–323. DOI: 10.1016/B978-0-12-381328-2.00013-4.

20. Kent, A. 'Huntington's disease'. *Nurs Stand*. (2004) 18(32), 45–51; quiz 52–53. DOI: 10.7748/ns2004.04.18.32.45.c3596.

21. Wanker, E.E. *et al.* 'The pathobiology of perturbed mutant huntingtin protein-protein interactions in Huntington's disease'. *J Neurochem*. (2019) 151(4), 507–519. DOI: 10.1111/jnc.14853.

22. Soares, T.R. *et al.* 'Targeting the proteostasis network in Huntington's disease'. *Ageing Res Rev*. (2019) 49, 92–103. DOI: 10.1016/j.arr.2018.11.006.

23. Nopoulos, P.C. 'Huntington disease: a single-gene degenerative disorder of the striatum'. *Dialogues Clin Neurosci*. (2016) 18(1), 91–98.

24. Podvin, S. *et al.* 'Multiple clinical features of Huntington's disease correlate with mutant HTT gene CAG repeat lengths and neurodegeneration'. *J Neurol*. (2019) 266(3), 551–564. DOI: 10.1007/s00415-018-8940-6.

25. Pandey, M. *et al.* 'Huntington's disease: the coming of age'. *J Genet*. (2018) 97(3), 649–664.

26. Johnson, E.B. *et al.* 'Huntington's disease: Brain imaging in Huntington's disease'. *Prog Mol Biol Transl Sci*. (2019) 165, 321–369. DOI: 10.1016/bs.pmbts.2019.04.004.

27. Zeun, P. *et al.* 'Fluid and imaging biomarkers for Huntington's disease'. *Mol Cell Neurosci*. (2019) 97, 67–80. DOI: 10.1016/j.mcn.2019.02.004.

28. Hong, E.P. *et al.* 'Huntington's Disease Pathogenesis: Two Sequential Components'. *J Huntingtons Dis*. (2021) 10(1), 35–51. DOI: 10.3233/JHD-200427.

29. Coppen, E.M. *et al.* 'Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease'. *Drugs*. (2017) 77(1), 29–46. DOI: 10.1007/s40265-016-0670-4.

30. Wyant, K.J. *et al.* 'Huntington's Disease-Update on Treatments'. *Curr Neurol Neurosci Rep*. (2017) 17(4), 33. DOI: 10.1007/s11910-017-0739-9.

31. Richard, A. *et al.* 'Deutetrabenazine in the treatment of Huntington's disease'. *Neurodegener Dis Manag*. (2019) 9(1), 31–37. DOI: 10.2217/nmt-2018-0040.

32. Dean, M. *et al.* 'Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease'. *Drug Des Devel Ther*. (2018) 12, 313–319. DOI: 10.2147/DDDT.S138828.

33. Barker, R.A. *et al.* 'Huntingtin-lowering strategies for Huntington's disease'. *Expert Opin Investig Drugs*. (2020) 29(10), 1125–1132. DOI: 10.1080/13543784.2020.1804552.

34. Bashir, H. 'Emerging therapies in Huntington's disease'. *Expert Rev Neurother*. (2019) 19(10), 983–995. DOI: 10.1080/14737175.2019.1631161.

35. Denis, H.L. *et al.* 'Antibody-based therapies for Huntington's disease: current status and future directions'. *Neurobiol Dis*. (2019) 132, 104569. DOI: 10.1016/j.nbd.2019.104569.

36. Vachey, G. *et al.* 'CRISPR/Cas9-Mediated Genome Editing for Huntington's Disease'. *Methods Mol Biol*. (2018) 1780, 463–481. DOI: 10.1007/978-1-4939-7825-0_21.

37. Estevez-Fraga, C. *et al.* 'Therapeutic strategies for Huntington's disease'. *Curr Opin Neurol*. (2020) 33(4), 508–518. DOI: 10.1097/WCO.0000000000000835.

38. Jensen, M.P. *et al.* 'Disease-Modification in Huntington's Disease: Moving Away from a Single-Target Approach'. *J Huntingtons Dis*. (2019) 8(1), 9–22. DOI: 10.3233/JHD-180320.

39. Wild, E.J. *et al.* 'Therapies targeting DNA and RNA in Huntington's disease'. *Lancet Neurol*. (2017) 16(10), 837–847. DOI: 10.1016/S1474-4422(17)30280-6.

40. Jabłońska, M. *et al.* 'Pridopidine in the treatment of Huntington's disease'. *Rev Neurosci*. (2020) 31(4), 441–451. DOI: 10.1515/revneuro-2019-0085.