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Huntington's Disease: A General Overview

Ni Mo

Teachers College, Columbia University, New York,10027

nm3474@tc.columbia.edu

Abstract. This article overviews Huntington's Disease (HD), emphasizing the development of neuroimaging biomarkers, pathogenesis discovery, and clinical treatment. The fundamental knowledge of HD includes its definition, diagnosis as an etiological subtype of neurodegenerative diseases in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), clinical neuropsychiatric symptoms, and social impact. The development of neuroimaging biomarkers is discussed with different developmental stages of HD. Mental health issues in the HD population including depression, anxiety, and psychosis were reviewed. The suicidal rate in this population is alarming, indicating the necessity to make both medical and mental health services available. Clinical treatments, including pharmacological and non-pharmacological, are overviewed with the timeline from now till the future. Recommendations are given for refining current research and future research design regarding neuroimaging biomarker exploration, early diagnosis, and potential treatment investigation. This review can provide some guidance to the development of more advanced diagnostic tools and effective treatments for this population.

Keywords: Huntington's Disease; neurodegenerative disorder; cytosine-adenine-guanine repeat disorders, movement disorders.

1. Introduction

Huntington's Disease (HD), a rare neurological disorder, is due to recurrent cytosine-adenine-guanine (CAG) in the Huntingtin gene. The disease's clinical manifestations include dementia, behavioral and mental abnormalities, and undesirable movements. In the Caucasian population, HD as a rare neuropsychiatric disorder affects 5–10 people per 100,000 [1]. Symptoms typically onset in middle age, while the disorder can manifest anytime from infancy to senescence [2]. When juvenile HD first appears in teenagers, it causes learning disabilities and behavioral abnormalities in those under twenty. As the illness worsens, chorea affects every muscle in the body and causes significant psychomotor retardation. Patients suffering from psychiatric symptoms and cognitive decline require round-the-clock care and eventually die from pneumonia or suicide, Mild neurocognitive disorder, delirium, and major neurocognitive disorder are the three syndromes that make up the neurological disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1]. The expansion of the huntingtin gene with 36 or more CAG trinucleotide repeats is a sign of an etiological mutation. It is etiologically diagnosed and classified as a subtype of Major and Mild NCD in DSM-5 after the syndrome diagnosis [3]. Because the DSM-5 uses the same terminology to define different neurocognitive disorders, and clinical features among diseases show non-specificity, exclusionary etiological criteria for diagnosing different subtypes of neurocognitive disorders are required. The application of biomarkers increases certainty while making the clinical classification, and neuroimaging is essential for determining the vascular and frontotemporal degenerative etiology. Thus, finding the neuroimaging biomarkers corresponding to different stages of HD progression increases the accuracy of categorizing the subtypes of neurodegenerative diseases through DSM-5 [3].

HD has hallmarks of motor dysfunction, cognitive impairment, and psychiatric symptoms. According to a recent study, psychiatric symptoms such as dysphoria, agitation, irritability, apathy, and anxiety are experienced by almost all patients with HD. HD frequently causes affective disorders and associated symptoms, and depression always coexists with the disease's progression in HD cases [4].

The high rates of attempted suicide and suicide among HD patients, suspected patients, and their relatives are further contributed to by those clinical symptoms. Several of those patients committed suicide because of depression [5].

CAG triplets repeat expansion in HTT causes HD, encoding expanded polyglutamine into the huntingtin protein. Longer CAG repeats indicate an earlier onset of disease, and those with 40 or more repeated CAG are linked to nearly full penetrance by age 65. Although the exact molecular pathogenesis mechanism is unclear, abnormal protein aggregation and conformation, undegraded toxic N-terminal fragments involved in the cell-autonomous and cell-cell interaction mechanisms are consistently postulated, offering potential targets for treatments' development. A major clinical challenge for tracing the progress of HD and developing treatment is the definition of endpoints, which captures the change in patients' brains when the clinical signals are too subtle to be identified. To understand the changes to neural anatomy and functions across stages of HD more, current research focuses on identifying the neuroimaging biomarkers in HD. The hyperkinetic movement caused by HD, e.g., tics, chorea, and dystonia, are treated with medications. Non-pharmacological interventions are relatively low-cost and low-risk and are undergoing the evaluation process as considering using them adjunctive to pharmacotherapy, including music therapy, exercise, dance, etc. It is currently difficult to generate an effective treatment for the cognitive component of HD. Researchers are focusing on reducing the current medication's side effects and exploring potential treatments that can delay the onset, slow progression, or reverse the ongoing process of HD [6].

Former studies around HD mainly focus on discussing one specific aspect of this disease, such as neuroimaging biomarkers, pathogenetic, and treatments, or presenting a general overview. However, studies focusing on the general knowledge of HD neglect the neuropsychiatric symptoms manifested during the progression of the disease and its related social impacts. While discussion of neuroimaging biomarkers and pathogenetic of HD are generated in previous research, different research uses various neuroimaging methods and clinical models. The neuroimaging biomarkers' detection corresponding to different disease progression stages and common features of molecular pathogenesis hypothesis among studies are rarely collectively mentioned. To fill the comprehensive gap in understanding HD as a neurodegenerative disorder, this paper overviews the results from fourteen previous research focusing on detecting neuroimaging biomarkers of HD and discussing the change in neuroimaging biomarkers following the four stages of disease progression. Besides, common features of different molecular pathogenesis theories of HD are mentioned alongside the neuropsychological symptoms, social impacts, and clinical treatments of this disease. Suggestions and recommendations for future research in this field are provided.

2. Methodology

This paper is an overview of HD based on literature reviews collected from Google Scholar, PubMed, and the Lancet platform. The primary sources for discussing the fundamental knowledge and clinical symptoms of HD are two review papers by Roos and Walker respectively [1-2]. The diagnostic category of HD and the related discussion of etiology subtypes of neurocognitive disorder in DSM-5 is provided [3]. The discussion of pathological mechanisms is based on the research of molecular pathogenesis and clinical intervention of HD [7]. The overview of the neuroimaging biomarkers is based on the neuropathological classification of HD and the development of biomarkers for it [8-9]. The primary source of reference for the general discussion of clinical development comes from the research of HD's treatment, which provides insights into current and potential new pharmacological and non-pharmacological treatments [10].

3. Results and Discussion

3.1. Neuroimaging Biomarkers

The majority of research into neuroimaging biomarkers for HD is based on Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), tracking the progression of the disease from stage 0 to stage 3 (that is, preHD versus earlyHD, or preHD distant from expected motor onset versus preHD near expected motor onset). Caudate volume in the HC population is 22% lower than in the matched population, according to earlier research using PET to measure local dopamine D2/D3 receptors availability. In the caudate and putamen, raclopride binding was 20–35% less than in the preHD group compared to the healthy controls. The average annual reduction in binding of an HD sample is approximately 5.4% within the caudate and 4.2% within the putamen. The caudate raclopride binding and volume both revealed a 2-3 percent reduction annually. An additional study that uses 18F-Fluorodeosyglucose (FDG) PET to assess regional FDG uptake to gauge regional glucose metabolism showed mean losses of 1.35% in HC and one and a half percent in preHD over a 2.5-year period [11].

As the most researched neuroimaging technique in HD, MRI is the basis for multiple studies of volumetric investigation of identified brain structures. Studies that evaluate the caudate nucleus via 1.5/3T MRI reveal volume loss specific to HD, with an annualized effect size (Cohen's d) ranging from 2.0 to 7.0 in manifest HD and from 0.27 to 3.0 in preHD. Putaminal volume change is assessed in seven studies using 1.5/3T MRI, and the volume loss estimates HD motor diagnosis as it shows greater volume loss compared to any other brain volumetric data. The early HD population showed larger effect sizes when compared to the pre-HD population. The highest value is shown by the intermediate group with Cohen's d of 0.58, and a smaller effect size appears as patients are in the stage close to motor diagnosis with a value of 0.53. Brain/caudate boundary shift integral T1 MRI was utilized to demonstrate that early HD patients have a large effect size compared to HC, with a Cohen's d that ranges from zero-point-nine to one-point-six [11].

Due to the significant volume loss of caudate or putamen across the stages of disease progress, MRI-based volumetric examination regarding the putamen and caudate are presently the best neuroimaging biomarkers for indicating the corresponding stage prior to the clinical motor diagnosis. Due to its prominent appearance after the structural alteration in HD, striatal atrophy is an appealing indicator of the disease's progression, as it correlates with both the length of the CAG repeat and the anticipated years since motor diagnosis. However, none of the neuroimaging biomarkers is validated to act as a signal to reflect pathological processes or disease-modifying effects [11].

3.2. Etiology

The expanded $(CAG)_n$ tracts that contain a polyglutamine segment cause significant cell loss in patients' striatum and neocortex. The HD-causing CAG expansion (i.e., Htt^{ex}) in exon-1 contains a polyglutamine segment beginning seventeen residues starting at the N-terminus. In-vitro evidence suggests that polyglutamine aggregates through creating trimers, oligomers, and dimers. Patients with 36 CAG repeats manifest HD, and those having 36-40 CAG repeats exhibit an HD phenotype; fewer persons have symptoms at thirty-six repeats and cases with no symptoms with forty repeats are rare [2]. According to research by Allan J. et al., there are multiple theories regarding the pathophysiology of HD, such as the promotion of apoptosis, toxicity aggregation, catastrophic crosslinking, transcriptional chaos, disrupted partners, and metabolic compromise. The expanded polyglutamine tract of Htt causes conformation changes, which further trigger pathogenic events involving proteolysis, homotypic aggregation, or heterotypic associations. Numerous pieces of evidence indicate that Htt^{ex} is responsible for the pathology; furthermore, that Htt^{ex} only affects the striatal medium spiny GABA projection neurons; and that the disease indicates cellular dysfunction prior to cell death [11]. Despite the unknown mechanism underlying polyglutamine aggregation and its link to selective neuronal dysfunction in HD and neurodegeneration, a number of important aspects of HD pathogenesis are known. Mutant HTT is prone to create atypical conformations as β-sheet structures,

and prolonged mutant huntingtin aggregates overcome the cells' ability to degrade via proteasomes or autophagic vacuolization, leaving unmanageable aggregated proteins. Those shortened version of HTT results in poisonous N-terminal fragments, and cellular localization, conformational alterations, clearance, and aggregation propensity are the means by which post-translational modification of HTT affects toxicity. The nuclear translocation of mutant HTT generates protein's harmful effects, and both HD patients and research models have disrupted cellular metabolic pathways. The intracellular pathogenesis of HD involves mutant HTT with the expanded polyglutamine repeat changes its conformation and interferes with the cellular trafficking of BDNF. The mutant HTT leads to reduced transcription of BDNF and nuclear-encoded mitochondrial proteins by interfering with gene transcription through PGC1a [7].

In addition to its toxic function, mutant huntingtin has a predominant adverse effect, interfering with the normal wild-type huntingtin. Cell-cell interactions are also involved in the pathogenesis of HD disease. Huntingtin mutations may impair neurons or glial function. In transgenic mouse models of HD, mutant huntingtin also interferes with axonal transport and neurotrophic factors in corticosteroid neurons, causing intrinsic dysfunction of striatal neurons. The exact cell mechanisms underlying the onset of HD and the reason for the long period of disease onset remain unknown, and researchers are still on their way to exploration. The major challenge for biologists to discover the underlying molecular mechanisms is the unparalleled disease onset process comparing the rapid-onset disease in those two research models (i.e., Htt^{ex} -ex-pressing transgenic mice and engineered cells) to the slow-onset disease in humans [10].

3.3. Psychiatric Symptoms and Social Impact

Aggression, impulsivity, depression, anxiety, apathy, psychosis, substance abuse, and sex disorders are among the behavioral and mental health issues associated with HD. One of the serious consequences of HD is death or suicide. Compared to the general population, HD patients are almost three times as likely to commit suicide in the age range from 10 to 49 years, while in the age group of 50-69, the suicide rate is 23-fold higher than individuals with typical development. Suicide appears to be four times more prevalent within suspected HD disease patients than among those diagnosed, suggesting that patients are especially susceptible to suicide at the initial phase of the disease [5]. The suicide frequency is higher in HD patients and their relatives than typically developing individuals in US. Of 2893 experimental subjects, 205 subjects reported suicide as the cause of death [12]. Another research by Farrer et al. presents that five-point-seven percent of deaths among HD-affected individuals were due to suicide, and at least one suicide attempt was made by 27.6% of patients [13]. Based on the high risk of suicide and attempted suicide among HD patients, suspected patients, and their relatives, opportunities to discuss feelings about the disease and psychological support from the physician or genetic counselor are necessary after the initial evaluation of this disease, especially for patients who have a family history of the disease.

Female patients with apathy and early dementia neglect their home and children. Married patients were subsequently divorced or separated due to social interaction issues, sexual aberrations, and intellectual barriers. Among the sample of 102 patients, there are at least 172 children at risk as potential carriers of the Huntington's gene. Besides the genetic issue, there are 17 cases of serious neglect of children and nine offenses of extreme violence towards children, including attempted infanticide. Unaffected siblings became victims of HD patients' disturbed environment, as ninety-three out of one-hundred-and-fifty passed away young, develop psychosis, or suffered from psychopathy, divorce, chronic alcoholism, and criminality [14]. Patients tend to be unemployed due to ataxia and dysarthria; male patients drift down from the social scale and are primarily unemployed when they have the disease. Although the assessment of alcoholism was probably underestimated due to the incomplete histories and misleading information from relatives in Dewhurst's research, it reports about 20% of alcoholism cases among the patient sample. There are other cases presenting patients convicted of offenses such as assault, offenses against property, cruelty to children, and malicious damage [14].

3.4. Diagnosis & Clinical Treatments

The prodromal illness that precedes HD is primarily diagnosed as psychoneurosis, personality disorder, affective state, and sub-normality. The average age when HD onset occurs is between 37 and 54. Violence, psychological and physical decline, hallucinations of trepidation, and depressive symptoms with suicidal ideas or actions, are the primary causes of admission [14]. To develop effective treatments for hyperkinetic movement disorders, e.g., chorea, dystonia, and tics, researchers investigate relevant medications. When selecting medications, it's important to take behavioral strategies, cognitive interventions, alternative therapies, and complementary treatments into account as they can assist with managing HD symptoms. If treatment for chorea is needed, tetrabenazine (TCZ), amantadine, or riluzole are taken into consideration. Research has demonstrated that TBZ, the sole treatment for HD approved by the US Food and Drug Administration, is highly effective in controlling chorea. It does this by selectively depleting dopamine in the caudate nucleus, putamen, and nucleus accumbens, and also by reversibly blocking the type II central vesicular monoamine transporter. However, several potential side effects are attached to the usage of TBZ, including akathisia, depression, dizziness, fatigue, or parkinsonism. It has been shown that depression can be exacerbated by TBZ, potentially causing suicidal ideation. Aripiprazole was found to be capable of reducing chorea, but it has the potential association with akathisia and tardive dyskinesia. Amantadine considerably lessens chorea in HD patients; however, it may also make them more agitated and aggressive. Dopamine agonists have been found in some studies to lessen the motor symptoms associated with HD. The reported symptomatic effects of dopamine agonists are primarily related to sedative properties, despite the lack of a clear pharmacological justification for their application in the chorea treatment [6].

Patients suffering from akinetic HD may find relief from levodopa, amantadine, and other antiparkinsonian drugs. Injections of botulinum toxin are taken into consideration for the Westphal variant, typical presentation, and focal dystonia linked to HD. There is a dearth of research on potential novel treatments for HD, such as using PBT2 to modify copper reactions with abnormal proteins and halt further brain cell deterioration. In addition, previous research has shown that PBT2 may improve motor function and control in animal models of HD through reducing the amount of neurodegeneration in brain cells. The possibility of reducing negative effects at peak dosage is investigated by researching the deuterated type of TBZ. Current research focuses on coenzyme Q10, creatine, and the extract of green tea polyphenon (2)-epigallocatechin-3-gallate, as it is critical for discovering a treatment that will postpone the start of HD and slow or reverse disease progression, and research has demonstrated that cannabinoids can treat HD irritability and chorea [6]. Besides, non-pharmacological interventions, adjunctive to pharmacotherapy, are worthwhile to be evaluated and noticed. Physical activity, dancing, therapeutic music, and playing video games are potential interventions that could improve gait and balance. Considering other spectra of interventions, current studies explore the injection of RNA into the basal ganglia or delivered via a viral vector to reduce the mhtt [6].

4. Conclusion

In summary, the HTT gene exon one's CAG repeat expansion serves as a genetic diagnostic biomarker for HD. People with CAG repeats over forty show the full spectrum of clinical symptoms. HD patients usually suffer from motor disturbance, cognitive dysfunction, and multiple psychiatric symptoms. Severe depression progresses with the development of the disease, leading to patient suicidal ideas. The suicide and attempted suicide rates are higher in HD patients and their relatives compared to the normal population. The disease also causes negative social impacts, including neglect and violence towards family members, increased unemployment rate, and increased alcoholism and criminal cases. Considering HD's pathogenesis mechanism, essential features are identified through previous research, including mutant HTT's abnormal conformation, aggregation, toxic N-terminal fragment from truncated HTT gene, and impaired cellular metabolic pathways, specifically causing the decreased BDNF transcription and nuclear-encoded mitochondrial proteins. An MRI-based

volumetric decrease in the caudate or putamen is the most effective neuroimaging biomarker for monitoring the disease progression. Current pharmacological interventions addressing chorea include TCZ, amantadine, and riluzole. The application of PBT2 to reduce the neurodegeneration and coenzyme Q10 (2CARE), CREST-E, and green tea extract for slowing down the disease progression is undergoing exploration. Non-pharmacological treatments such as motor training programs, psychotherapy, and RNA interventions are valuable research targets nowadays and in the future.

The recommendation for future research related to biomarker detection is to notice the comorbidity of other disorders while sampling the participants, as it would interfere with the brain structure change. Developing neuroimaging biomarkers using a deep neural network (DNN) for identifying biomarkers can help with the early diagnosis process of HD and further assist the development of pharmacology for early disorder on-set prevention or slowing down the disease's progression. Besides, identifying the neuroimaging biomarker benefits the development of treatments targeting different neurological changes, which should be designed corresponding to various stages of HD progression. Regarding the research on the socio-psychiatric impact of HD, researchers might consider applying a larger sample to make better inferences about the whole population having HD. Furthermore, psychiatric symptoms should be considered when clinicians suggest medications and non-pharmacological therapies should be considered alongside pharmacological treatment for a better therapeutic outcome. Considering the non-pharmacological treatments, specific training for the behavioral management of HD patients should be constructed in psychiatry and neurology programs to help patients overcome motor dysfunctions, while genetic counseling and evidence-based psychological treatment should intervene to reduce the negative impact of psychiatric symptoms manifested due to HD.

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