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Potential strategy for treating Huntington's disease with gene therapy

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ABSTRACT:
Huntington's disease is a neurological condition for which there is no currently therapeutic intervention. Gene therapy can be considered as the one possible way to treat the Huntington's disease. Several factors contribute to the development of Huntington's disease, including excitotoxicity, impairment of proteostasis, mitochondrial dysfunction, oxidative stress, transcriptional dysregulation, reduced production of brain-derived neurotrophic factor, glial cell dysfunction, and neuroinflammation. Clinical manifestations are the primary three indication that a person has Huntington's disease includes motor, cognitive, and mental disorders. Chorea, which is characterized by rapid, unpredictable, involuntary, and irregular movements, is the main motor sign of Huntington's disease. As Huntington's disease progresses, symptoms of Parkinson's disease such bradykinesia, rigidity, and dystonia begin to appear and get inferior in the final stages of the disease. Executive functioning, procedural memory, and psychomotor abnormalities are among the cognitive symptoms that typically manifests years before additional symptoms do.

Keywords: Huntington's disease (HD), Htt (Huntingtin Gene), mHtt (Mutant Huntingtin Gene), N-methyl-D-aspartate receptors (NMDARs), proteostasis, brain-derived neurotrophic factor (BDNF), oxidative stress, proteostasis, gene therapy, reactive oxidative stress (ROS) mini mental state examination (MMSE)

I. INTRODUCTION:

The Huntingtin gene (Htt) was found (1993) by the Huntington's disease joint research group (25). Research groups were actively exploring various avenues for the Huntington's disease treatment. For this illness, Huntington's Disease, a few neuroprotective treatments have been introduced (26). Out of broader range of medications, only a few medications have undergone clinical testing; as a result, only unsuccessful medications are utilized for treatment of this disease. Unfortunately, medicines sometimes provide only mild and transient relief, with few positive effects. Diseases will assuredly worsen, and treatments may become less effective. In addition to addressing the three sets of symptoms that HD patients experience (motor, cognitive, and psychiatric), the optimum treatment should also attempt to decrease or halt the progression of these symptoms either by reducing or caseation of neuronal degeneration. Analysing the best administration strategy is a further challenge in the development of any medicine. A simplified strategy to gene therapy delivery is necessary to maximize its effectiveness. This research will evaluate medications presently undergoing testing in HD animal models and the administration of such medications via viral vectors (27). HD prevention relies on two main approaches: 1) using growth factors to provide vital nutrition and support for cell survival, and 2) reducing or removing the mutant huntingtin protein. It has been determined that neurotrophic factors are safe for use in humans after pre-clinical testing in animal models and the advancement of a few candidates to clinical trials for HD, a similar neurological disorder. Do neurotrophic factors still have the potential to be helpful to patients considering promising breakthroughs in treatments like RNA interference, which directly target the underlying genetic problems that underlie HD? This review will discuss the above-mentioned treatments as well as the most recent and effective ways to provide neurotrophic factors and siRNA to people with HD as well as to animals with the disease. (1)

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II. PATHOPHYSIOLOGY OF HUNTINGTON'S DISEASE:

To understand better about the complex processes by which mutant huntingtin (mHtt), an aberrant protein, causes extensive cellular degeneration and inhibits synaptic function in HD, several research teams move their attention from discovering the genetic aberration. To understand these intricate systems, they used chemical simulations, (28) different models of genetic models, (29) or sophisticated cell lines that mimicked the intercellular correspondence (30) and circuitry seen in the human brain. Numerous harmful pathways have been identified, (31) but this assessment is not intended to provide a full list of all of them. As a result, they are briefly described here. (2)

2.1. Excitotoxicity:

The thalamus and brain supply most of the glutamatergic input to the striatum. The actions of glutamate are mediated through N-methyl-D-aspartate receptors, amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors, and kainite receptors. The two GluN1 (formerly NR1), two GluN2 (or NR2), and/or two GluN3 (or NR3) subunits make up the tetrameric complexes that make up NMDARs. Mutant Htt disrupts the GLuN2B gene's transcription, changing the receptor's structure and elevating its glutamate sensitivity. Additionally, the organization of NMDARs is disrupted by the impaired interaction between mHtt and the postsynaptic density of the scaffolding protein 95 (PSD95), resulting in a greater number of receptors outside the synapse (2). Based on recent studies, striatal neurons that express full-length mHtt are inherently more sensitive to stress. This is because initially elevated NMDAR activity, particularly that involving the NR1/NR2B subtype, causes an increase in intracellular calcium levels and the catabolic enzymes' activation. These events can be the first in a series that leads to neurological dysfunction. The unique toxic effects of mHtt interact with the reduced mitochondrial activity in striatal neurons to cause cellular malfunction and activate the caspase cascade, which further exacerbates cellular damage. Our theory, based on the results, is that changed in mHtt interactions or functions, which initially cause an increase in NMDAR activity, might repeatedly subject neurons to sub-lethal shocks. Furthermore, the local activation of Htt-cleaving proteases by these sub-lethal shocks brought on by NMDAR over-activation may enhance its nuclear localization and result in transcriptional dysregulation. (3)

2.2. Impairments of proteostasis:

Linear amino acid chains are regularly used to create proteins, which chaperones help fold into three-dimensional structures. The ubiquitin-proteasome system i.e., UPS either targets misfolded proteins for destruction or causes them to refold into their proper shape. Chaperone availability is decreased by mutant Htt aggregates, which enhance aberrant protein folding. It has been discovered that UBE3A is a unique enzyme with -amine E2 activity. With time, this enzyme's ability to preferentially target Htt fragments for ubiquitylation and subsequent destruction decreases. The late start of this genetic illness may be explained by this phenomenon. The systemic ubiquitylation dysfunction in HD, an essential component of proteostasis, is also complex and progressive, affecting several biochemical pathways, including those connected to the ubiquitin proteasome system and autophagy, which oversee breaking down protein aggregates. Understanding the molecular processes associated to proteostasis that are involved in Huntington's Disease pathogenesis provides significant understandings of how the illness develops in HD and opens possible treatment paths. (4)

2.3. Mitochondrial dysfunction:

For most of the energy they require, neurons rely on mitochondrial oxidative phosphorylation. Due to this reliance, the conflicting processes of mitochondrial fusion and fission are precisely done to regulate the size, shape, and quantity of mitochondria within the cells. Different proteins control each of these processes: dynamin-related or dynamin-like protein 1 (Drp1) and dynamin2 (Dnm2) control fission, whereas mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1) control mitochondrial fusion (2). HD, a condition marked by the growth of polyglutamine repeats that mostly striatum and cerebral cortex is impacted, has pathological processes that are largely caused by mitochondrial malfunction. Our knowledge of mitochondrial roles inside eukaryotic cells has developed over time beyond their acknowledge function as true cellular powerhouses, notably in neurons. In fact, mitochondria are currently involved in the production of a variety of metabolites in addition to acting as dynamic organelles that may fuse and fragment to maximize bioenergetic efficiency. They actively move along microtubules, interact with the endoplasmic reticulum to control intracellular calcium levels, produce free radicals, and take part in cellular functions associated with programmed cell death. (5)

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2.4. Oxidative stress:

Oxidative stress is characterized by a disparity between the generation of reactive oxidative species (ROS) and the ability of the biological system to successfully remove these compounds (2). Oxidants and antioxidants are in equilibrium. This equilibrium permits oxygen radical in reaction and other oxidants to directly change certain amino acids (such as cysteine) on signalling proteins to carry out essential regulatory tasks. The precise spatial, amplitude, and temporal regulation of oxidant concentrations is necessary for these signalling activities. Oxidative stress, on the other hand, is a harmful state that develops when oxidants outpace antioxidants (6). Reactive oxygen species, or ROS, are primarily produced by mitochondria because, even in normal conditions, they can permit 2% of electrons to "escape" from the electron transport chain. As previously shown, the generation of Reactive Oxygen Species greatly increases in the presence of dysfunctional mitochondria, aggravating that condition. As a result, the mitochondrial permeability transition pore opens, resulting in a calcium surplus and ultimately start of the apoptotic process (7). Additionally, ROS have the capacity to activate immune cell receptors, causing a variety of cytokines to be released. (6) In turn, these cytokines regulate macrophage polarization toward the pro-inflammatory M1 phenotype, which starts the process of neuroinflammation (8). This behaviour is particularly observable when considering conditions such as HD, amyotrophic lateral sclerosis (ALS), or even stroke, where neuroinflammation (9), which is playing an increasingly important role, is being given more attention. (2)

2.5. Transcriptional dysregulation:

According to study, mutant huntingtin (mHtt) interacts with several transcription factors and coactivator proteins as to disrupt transcription and the function of vital proteins. In one such connection, mutant Htt and the CBP (CREB binding protein)/p300 dimer, their acetylase activity is inhibited. The Nrf2-ARE (antioxidant response element) pathway, which controls the transcription of various antioxidant proteins and enzymes, is interfered with because of this inhibition, which is crucial for the cellular localization and stability of nuclear factor-erythroid 2-related factor-2 (Npf2) (10). Additionally, mutant Htt lowers the transcription of peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) and alters the CREB/TAF4 transcriptional pathway in striatal neurons. Repressor element 1 (RE1)—silencing transcription factor (REST) can block target genes like the brain-derived neurotrophic factor (BDNF) gene because mutant Htt promotes REST's nuclear translocation. Pro-apoptotic proteins including Bcl2-associated X protein (BAX) and p53-increased modulator of apoptosis (PUMA) are upregulated because of mHtt's binding to Php53 and enhancing its transcriptional activity. (2)

2.6. Impaired BDNF synthesis and transport:

The function of cortico striatal synapse and the GABA-anergic medium-sized spiny striatal neurons' survival that perish in HD depend on cortical BDNF synthesis. In tests, endogenous BDNF levels were further lowered artificially, which resulted in a later age of onset and worsened motor dysfunction. These investigations examined the effects of BDNF depletion in HD animals. The neuropathology of the brain as it has been observed is in line with structural alterations in the brain, supporting the crucial part played by BDNF in the selective striatal neuron's degeneration (11). BDNF mRNA is rather weakly expressed in striatal neurons. However, striatal medium spiny neurons (MSNs) need to acquire significant quantities of BDNF for essential trophic maintenance, and this supply mostly comes from cortical neurons via the cortico-striatal tract (12). REST/NRSF (neuron-restrictive silencer factor) builds up in the nucleus of cortical neurons because there is an interaction between mutant Htt (mHtt) and REST, which subsequently prevents the transcription of BDNF (13).

2.7. Dysfunction of glial cells:

Astrocytes also exhibited intracellular mHtt aggregates that may suppress the expression of inwardly rectifying K+ channels, resulting in a reduction in membrane potential and conductance. These modifications modify how sensitive astrocytes are to neuromodulators. (2)

Glial cells are critical to the formation and proper function of brain networks. Nevertheless, these cells become dysregulated in many neurodegenerative diseases and may contribute to brain pathology. Glial cells in HD lose their usual activities and have neuropathic phenotypes. Additionally, the pathology and HD-related deficits in motor and cognitive function can be caused by the production of mutant huntingtin in specific glial cell types, suggesting that these cells may be involved in the aetiology of various elements of the illness. (14)

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2.8. Neuroinflammation in HD:

The pro-inflammatory cytokine genes are activated by mHtt, which enhances the microglia's responsiveness to activating signals. These signals are recognized by toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), which stimulate the downstream production of inflammatory cytokines (2). Numerous neurodegenerative diseases are characterized by neuroinflammation, which is defined by reactive gliosis and the creation of soluble inflammatory chemicals inside central nervous system. Unlike other neurodegenerative diseases, HD does not exhibit a large migration of peripheral immune cells into the brain [20, 25]. As a result, activated microglia and astrocytes are responsible for many inflammatory processes. While no reactive T cells have been found in the brains of HD patients, reactive astrocytes are present in those with pre symptomatic HD and are associated with the severity of the condition [24]. Reactive microglia are seen in the striatum and cortex of HD impacted the brains; two regions where postmortem investigations have revealed neuronal loss [25]. Positron emission tomography (PET) imaging can identify brain alterations in patients with early disease. Neuroinflammation can be detected using the translocator protein, which is typically generated at low levels in a healthy central nervous system. However, microglia and astrocytes upregulate translator protein expression in neuroinflammatory processes. In the striatum of people with HD, PET imaging reveals higher levels of the TSPO tracer, and this rise relates to the severity of HD symptoms. This increase is caused by microglia activation [30]. Additionally, the activation of microglia was seen in HD gene mutation carriers before they manifested symptoms [31], suggesting that it occurs prior to HD symptoms. Nevertheless, a second-generation translator protein tracer with a low signal-to-background ratio was used in these studies. In a recent research, patients with Huntington's disease (HD) underwent PET imaging using a new tracer with a high signal-to-background ratio. According to the study, whereas microglial activation is considerable in those with manifest HD, it is not in premanifest HD sufferers [32]. It is crucial to remember that this study had a significant flaw since the patient group was so tiny (15).

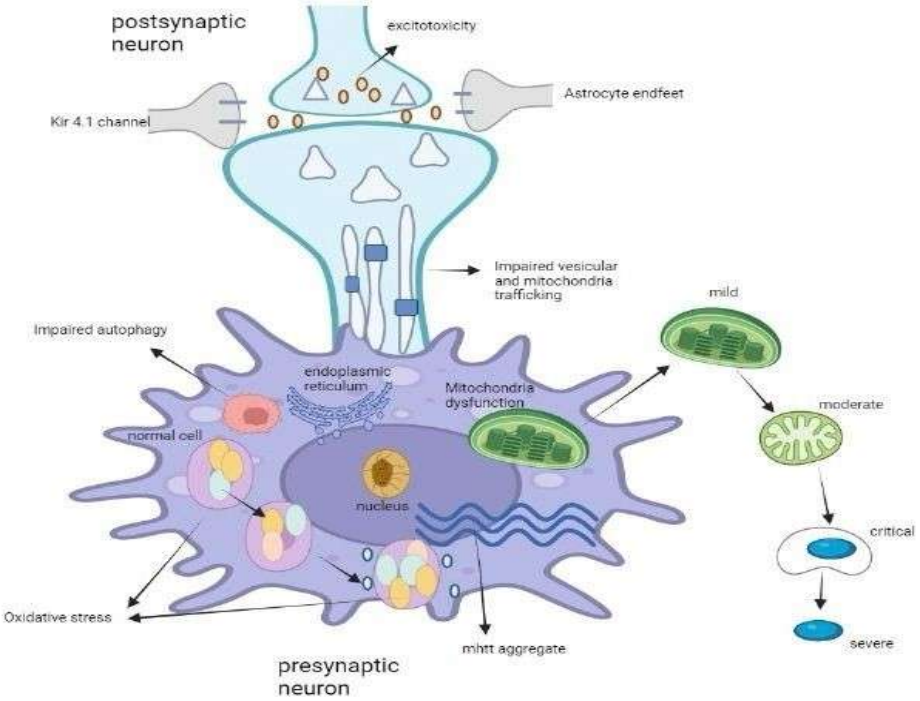

fig 1.1 An overview of Pathophysiology of Huntington's Disease

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III. CLINICAL MANIFESTATION:

There are three main symptom categories associated with HD, including motor, cognitive, and psychiatric symptoms. The primary motor symptom of HD is chorea, which is characterized by erratic, uncontrollable, and unintentional involuntary movements. While chorea is the hallmark sign of HD, additional motor symptoms including dysarthria, hyperreflexia, and abnormal eye movements are frequently seen as well. These symptoms may even start before chorea (17). Parkinson's disease symptoms such bradykinesia, stiffness, and dystonia start to appear as HD advances and become more severe in the later stages of HD (18). Additionally, patients report psychological symptoms such depression, anxiety, paranoia, anxiety disorder, interpersonal sensitivity, and obsessive-compulsive disorder (19) (20). These abnormalities are very common and can appear up to ten years before motor symptoms start to appear. These indications of HD might be the most distressing signs. HD sufferers are prone to mental instability, which commonly results in suicide, according to George Huntington's original description of the illness (21). Cognitive symptoms, which include executive dysfunctioning, procedural memory, and psychomotor abilities, usually manifest years before other symptoms (22) (23) (24). Patients are substantially more disabled by these non-motor symptoms than by the motor indications. Unfortunately, many treatments used today have little effect on the motor symptoms and are ineffective in treating the cognitive or psychological problems. (1)

IV. DIAGNOSIS:

As soon as the HD gene was identified, straightforward PCR-based methods for identifying the mutant allele were created (21). The CAG repeat was initially measured by measuring the PCR product's length, which included the CAG repeat together with the neighbouring CCG and CCT repeats, considering that there were two triplets in the CCT repetition and seven in the CCG repeat (22). Later research revealed that the CCG repeat may range in length from 7 to 12 triplets (24) and that the CCT repeat, which follows the CCG repeat (26), can range in length from 2 (common) to 3 (rare) triplets. To avoid the length of the CAG repeat, which is crucial in pre-symptomatic testing even more than in routine diagnostic testing, labs are now advised to employ a PCR assay in which the final product only contains the CAG repeat (25)(16).

V. TREATMENT:

5.1. Treatment of motor symptoms:

5.1.1. Chorea:

Due to the uncontrollable movements, patients with chorea frequently do not experience awareness or impairment. In such cases, it is essential to reassure the patients and their families and to educate them. Treatment for chorea is only necessary when it significantly compromises a patient's quality of life, functional capacity, or safety. Due to the early and selective degeneration of striato-GPe neurons, which are critical elements of the indirect route, chorea is more common in the early stages of Huntington's disease. The subthalamic nucleus is suppressed because of the indirect pathway's initial failure, which causes hyperkinetic behaviour (32, 33). Presynaptic depletion or D2 receptor blockage both reduce dopamine neurotransmission, which eventually results in less excessive movement. The basic idea behind the current pharmaceutical therapies for chorea is represented by this. Tetrabenazine (TBZ) is the only medication now approved by the Food and Drug Administration (FDA) for the treatment of chorea in HD patients. The central nervous system's vesicular monoamine transporter 2 (VMAT-2) is momentarily blocked by TBZ. VMAT-2 packages serotonin, dopamine, and norepinephrine into presynaptic vesicles; hence, when it is blocked, this process proceeds more quickly (32). While the resulting drop in dopamine levels relieves chorea, the drop in serotonin and norepinephrine may make symptoms of anxiety and sadness worse. (31)

5.1.2. Other motor manifestations:

The Westphal form of HD is a unique akinetic-rigid condition that is more likely to manifest in people with Huntington's disease who are diagnosed before the age of 20. While adults exhibit this symptom, there have been a few documented occurrences in the literature. (34, 35). About 65-85% of individuals with Huntington's disease in childhood and up to 55% of those who first develop the condition in their early 20s have this characteristic. Parkinsonism and dystonia are combined to form the main clinical symptom (96). Levodopa and dopamine agonist therapy have shown different degrees of efficacy in individual case reports (36, 37, 38). For this group of patients, we often choose levodopa over dopamine agonists due to thetendency to cause behavioural adverse effects. In this group, surgical procedures including bilateral GPi pallidotomies and DBS have been tried,

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but the results have been few and transient (39, 40).

The very infrequent incidence of cortical myoclonus is more commonly seen in those with juvenile-onsetthan in adults. In this situation, myoclonus is sensitive to actions and stimuli, and EEG testing may show related abnormalities. These individuals may respond well to therapy with valproic acid or benzodiazepines since the proposed mechanism is connected to a GABA deficit (41,42). HD is usually accompanied with dystonia, although there have been no clinical trials to assess the effectiveness of therapy in this setting. The botulinum toxin usage may be advantageous for people with severe or disabling segmental or focal dystonia.

The management of Huntington's disease (HD) may benefit from exercise-centred therapy given the lack of pharmacological treatment options. Physical therapy (PT) can be very helpful for diagnosing and treating concerns linked to gait irregularities, balance disorders, and the early-stage danger of falling. When daily activities become vulnerable by motor dysfunction, occupational therapists (OT) can help. Therapists and social workers may suggest making changes to the home environment and installing equipment to promote flexibility and safety(97). Speech pathologists can provide help at all stages of the disease by addressing issues including dysarthria and dysphagia in addition to physical therapy (PT) and occupational therapy (OT) for symptoms involving the motor symptom. Our advice is to start speech and swallowing treatment before significant dysphagia manifests so that behaviour and eating habits can be changed to reduce the risk of aspiration. (31)

5.2. Treatment of cognitive symptoms:

Memantine and cholinesterase inhibitors are used to treat other types of dementia, but there is not much data to support their use. In terms of cholinesterase inhibitors, rivastigmine may be the best option. Following both short-term and long-term treatment of rivastigmine, possible cognitive improvement has been shown by three small open-label trials (43,43). These results have drawn criticism even though the Mini-Mental State Examination (MMSE) is said to be insufficient in capturing the processing speed and frontal dysfunction abnormalities typical in patients with Huntington's disease. In one small-scale randomized placebo-controlled experiment that used more rigorous cognitive evaluations, individuals with Huntington's disease who took rivastigmine for six months showed a tendency toward improved verbal information recognition (43). There are even fewer studies to back up the usage of donepezil (44).

Given how much glutamate the cortex and thalamus input into the striatum, it is hypothesized that at least some of the neurodegeneration in HD may be brought on by excitotoxic damage. Memantine is a non-competitive antagonist of the glutamate receptor that helps to stabilize glutamatergic activity generally (45). Memantine is used as treatment of Alzheimer's dementia, but trials to determine how it affects cognition in Huntington's disease have not been conducted. Possibility of a neuroprotective effect with prolonged therapy was suggested by a single, open-label trial with a limited sample size (46); another research, however, have not supported this conclusion.

We cannot support the routine use of these drugs to improve cognition in Huntington's disease due to the paucity of strong supporting data (95). Instead, it is preferable to concentrate on encouraging actions such providing hints, limiting multitasking, and allotting sufficient time for mental exercises (31).

5.3. Treatment of psychiatric disease:

5.3.1. Suicide and Depression:

Depression can respond to therapy in a wonderfully favourable way, although this part of the condition is still frequently not appropriately addressed. A study of the 1,993 patient European HD cohort (REGISTRY) found that only 50% of persons who reported experiencing moderate to severe depression were using medication to manage their symptoms (47). According to a study done on the 1,993 patient European HD cohort (REGISTRY), medication was only used by 50% of individuals with moderate to severe depression to treat their symptoms (47).

The lack of strong data to guide decisions on pharmaceutical therapy for depression in Huntington's disease was recently brought to light by a comprehensive review (48). Three studies demonstrated the effectiveness of venlafaxine, an SNRI (serotonin-norepinephrine reuptake inhibitor), and specific serotonin reuptake inhibitors (SSRIs) on patients with this condition. Even though the research samples included non-depressed people, fluoxetine, and citalopram among the SSRIs both showed a tendency towards improvement in the HDRS (Hamilton Depression Rating Scale) (49,50). Venlafaxine XR exhibited improvement in depressive symptoms after 4 weeks of treatment (51). It is crucial to remember that this study dif-

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fered from normal studies for the treatment of depression in that it lacked control and was shorter in duration.

Although there is a paucity of published research on this topic, it is well known that Huntington's disease's patients frequently respond well to SSRIs and other traditional depression medications. Atypical antipsychotic drugs such olanzapine (52), risperidone (53), aripiprazole [54,55], and clozapine [56] have shown promising results in cases of treatment-resistant depression based on case reports and limited open-label case series. A case series suggests the use of long-acting risperidone injections as a safe and potentially beneficial solution in circumstances when medication adherence is problematic [57]. Additionally, it has been demonstrated that electroconvulsive therapy (ECT) can effectively cure depression in Huntington's disease patients who have failed previous therapies [58–59].

Suicidal inclinations are a serious problem for people with Huntington's disease (98). Suicide attempt risk is higher for people who have had or are currently experiencing depressive episodes (99). Approximately 20% of individuals with Huntington's disease reported having suicidal thoughts, and the prevalence of suicide attempts may be as high as 10% (47, 60]. People with Huntington's disease have a 4–8 times greater chance of committing suicide than the general population [61, 62]. When motor symptoms initially appear and as independence begins to decline, this risk becomes more obvious [60]. Lack of children, being single or divorced, living alone, a family history of suicide, little contact with others who have Huntington's disease, and being depressed are all factors that increase the risk [62]. A greater likelihood of suicidal thoughts is linked to anxiety, hostility/irritability, and a history of alcohol abuse [63]. In order to effectively treat behavioural problems and encourage support groups, it is necessary to focus on individuals who are socially isolated. (31)

5.3.2. Other behavioural symptoms:

Apathy differs from depressive symptoms in that it is characterized by a loss of drive and decreased goal-directed conduct. It occurs more frequently when the illness is more advanced [47]. It has been documented in almost 50% of significant cohort studies, while being less frequent than depression [62, 63]. Apathy caused by HD has no recognized effective therapies. All the drugs examined, including bupropion, bromocriptine, and amoxetine, failed to significantly improve the condition [64]. According to Curr's representation of Neurol Neurosci (2017) 17, you might think about lowering the amount of tetrabenazine or neuroleptics as the condition worsens if chorea occurs less frequently since these medications may impair motivation. In 10–50% of HD patients, obsessive compulsive disorder's symptoms may be present [63], although the knowledge guiding therapy is primarily based on case reports and expert opinion. [65-66]. SSRIs and clomipramine were mentioned as first-line therapy the most frequently in a poll of HD specialists. Only for individuals with minimal or no cognitive impairment has cognitive behavioural therapy been evaluated as a treatment option. Antipsychotics and mood-stabilizing antiepileptic medications, such valproate, topiramate, carbamazepine, and lamotrigine and were favoured by responders as adjuvant treatments (65). In 38–73% of patients, irritability and agitation are present [63], and additional investigations [62, 64] have verified this large range. Again, the only information currently available to direct therapy is case reports [67] and professional judgments. It is crucial to teach families and caregivers how to recognize triggers and behavioural methods to prevent outbursts in milder, non-aggressive situations. SSRIs may be useful in certain situations. Instead of using SSRIs, therapy with atypical antipsychotics and mood-stabilizing Antiepileptic Drugs is advised in situations of concomitant impulsivity, aggressiveness, or hypersexuality [68]. Although psychosis and delusions are less common in HD and have been seen in 3–11% of patients [63], they are more common in the later stages [47]. Although less common in HD patients, psychosis and delusions have been observed in 3–11% of cases [63], with a higher incidence in the latter stages [47]. Finally, whether or whether drugs are being utilized, cognitive and behavioural symptoms of the condition may react to a supportive, organized environment with routines and signals. Early identification and management of caregiver burden are crucial given that HD has a significant impact on young families. Social workers are playing important role in supporting these families and locating services like caregiving aid, respite care, counsellors, and financial support. (31)

VI. GENE THERAPY FOR HUNGTINGTON'S DISEASE:

Due to the complicated pathogenic implications of mutant huntingtin, a single post-translational treatment strategy as outlined is

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probably inadequate. The research focusing on the faulty gene itself is the most promising advancement in the hunt for a disease-modifying medication. Techniques for gene silencing are now being actively developed in HD. These include reducing or stopping the transcription of the mutant gene, as well as inhibiting its translation. Antisense oligonucleotides and RNA interference (RNAi) mechanisms are the most effective HD treatment options. By preventing mutant mRNA from being translated and lowering protein production, they might treat the illness at its root. But it would be imperative to safeguard the normal allele since, wild-type huntingtin plays a significant role in development and cellular function. Antisense oligonucleotides, which are tiny single-stranded molecules, are made with a complementary sequence to a particular pre-messenger Ribonucleic Acid (mRNA) or messenger RNA that oversees a disease. One type of ASO interacts with pre-mRNAs in the nucleus and activates RNAase H, an enzyme that breaks down the message before it can be translated. In this situation, the ASO is not broken down but is instead free to bind more pre-mRNAs. ASO may also interfere with ribosome translation by steric hindrance and other ways by binding to mRNA in the cytoplasm [69]. The basic premise is that neuro-degeneration may be delayed or perhaps stopped if synthesis of the aberrant protein can be reduced. The CAG repeat, single nucleotide polymorphisms (SNPs), or introns on the pre-mRNA can all be the target of an ASO in HD [70, 71]. ASO has been used in recent research that has improved HD-like pathology and motor symptoms in mouse models [74,75,76] and lowered human mHtt production of fibroblasts [71, 73]. These focused on exonic and intronic SNPs that were often extremely selective to the mutant allele and had no impact on the generation of wild-type Htt. In some of these studies, mHtt production continued to decline even months after the final treatment. There could be some difficulties. ASOs that target the HD CAG repeat may also silence genes that have related repetitions, particularly if the pathogenic allele has less than 40 repeats. To effectively target the aberrant allele, several ASOs would need to be utilized, and even then, only 80% of patients would be covered [70] individualized ASOs based on the patient's unique mutation and SNPs are a different possibility, albeit there is not yet a complete FDA process for this kind of individualized treatment. Additionally, ASOs require intrathecal administration since their present formulations do not allow them to pass the blood-brain barrier. Without a vector, they do penetrate the neurons and their nuclei [77,70], although it is unclear how much of them will reach the human striatum if administered through lumbar puncture [78]. This delivery strategy has been used before in people to treat ALS caused by SOD1 [79]. Ionis Pharmaceuticals is conducting an early phase study of an intrathecal Htt-directed ASO, although findings have not been made public yet [80]. RNA interference targets mRNA for degradation before translation by activating the RNA-silencing complex and cleaving the target with siRNA, or short interfering RNA or micro-RNA (miRNA) molecules. These short sequences cannot consistently degrade solely mutant mRNA because of their length. SNPs that are present in some Western and European HD populations can be targeted, but [81, 82]. To specifically target mutant Htt lacking such poly-morphisms, combinations of multiple siRNAs would be required. Although single stranded RNA (ssRNA) is longer and more stable than siRNA and can function similarly, it may only be effective against CAG repeats that are extremely long (over 100 in animal models), which are not present in human populations. Adeno-associated viral vector with an HTT-silencing miRNA was injected intraarterially to induce transduction in about 80% of the striatum, decrease HTT mRNA and protein by 50%, and enhance motor function in the YAD128 HD mouse model [83]. The inability of RNAi to enter cells in a naked condition is a significant present constraint; therefore, the requirement for a viral vector. It is currently unknown how far the two striata can disperse into the living human brain parenchyma because the approach calls for injection to both (93) They are degraded considerably more quickly than ASOs, which may lessen the possibility of damage but necessitates repeated treatments. This method has already been used in two human studies for different disorders [84, 85]. Two other methods of genetic modification have been put forth but have not been tried on people (94). By suppressing its expression, the first protein, zinc finger proteins (ZFPs), may be directed to the HD CAG repeats. Due to the repeat's closeness to the HTT gene is 5′ end, the ZFPs are selective to HTT while not cross-suppressing other poly-CAG-containing genes [78]. It reduced the synthesis of the mutant protein and mRNA by 95 and 78%, respectively, in R6/2 animal models [86]. However, viral delivery of this protein to the target cells is also required. The alternative method entirely silences the gene by editing away the mutation at the genome level using CRISPR-Cas 9, a relatively

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new technology. However, neither of these methods has been tried in a clinical setting [34].

VII. DISCUSSION:

Though the genetic mistake responsible for Huntington's disease was identified around thirty years ago, the disease's symptoms are the only things that can be treated with the current treatment alternatives, and there has been little advancement in that time [87]. The inability of currently known medicines to target targets, affecting primarily downstream processes, and permitting the progression of pathogenic cascades when they are not stopped [88] is perhaps their most significant flaw (92)The increasing focus in medicines which mHtt DNA and RNA targets offers up new, interesting possibilities and will probably lead to better results when paired with tactics targeting glutamatergic neurotransmission, BDNF signalling, or mitochondrial function. Additionally, because the bacteria in the intestines is altered in HD (like in other neurodegenerative diseases) [89], addressing it may increase the effectiveness of treatment [90]. The use of genetic therapies is still in its early stages. The security of non-selective mHtt lowering, the occurrence of off-target results in significant numbers of persons, and CRISPR security interventions are still areas of uncertainty [91]. Additionally, the requirement for invasive delivery might be a significant disadvantage [92], restricting adherence and access to therapy. However, given the promising recent advancements, a new age in HD therapy may be upon us shortly. (2)

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