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A Review on Huntington's Disease

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ABSTRACT

Huntington's disease (HD) causes advanced neurological degeneration that leads to death. It is inherited in an autosomal dominant manner, and individualities with a favorable family history can be tested for the presence of the HD mutation before developing the overt features that subjectively outline complaint onset. The conclusion can be made clinically in a case with motor or cognitive and behavioral disruptions with a parent diagnosed with HD and can be verified by DNA determination. In those cases, who are at threat for the complaint, a pre-manifest opinion can determine if they carry the gene. Although definite genetic tests have been available for about 20 years, ongoing pharmacological treatments do not avert or decelerate disease progression. The recent essential investigation identified potential new drug targets for treating Huntington's disease. Even so, there are clear challenges in understanding these discoveries into treatment strategies for these patients. There is no cure for the disease, and affected cases tend to be entirely dependent on their caregivers as the condition progresses. Thus, treatment is aimed at perfecting the quality of life and lowering complications.

INTRODUCTION

Huntington's Disorder (HD) is an autosomal dominant, neurodegenerative illness, generally occurring in a juvenile and midmost era. It is described by unique psychiatric challenges and advanced debilitation in cognitive function and motor control, directing to primitive decease. Huntington's complication is caused by a CAG reprise increment in the huntingtin (HTT) gene on chromosome 4 that codes for polyglutamine in the huntingtin protein. Symptoms evolve insidiously, as a movement complication manifests by the concise haul- the suchlike movement of the extremities, trunk, face, and neck (chorea), as personality changes or both. Fine motor incoordination and impairment of rapid eye movements are early features as the complaint progresses, the involuntary movements come more severe, dysarthria and dysphagia develop and balance is impaired. Opinion can be made clinically in a case with motor and cognitive and behavioral disturbances with a parent diagnosed with HD and can be verified by DNA determination. A pre-manifest opinion can determine if they carry the gene in cases at threat for the complaint. There is no cure for the complaint, and affected cases tend to be entirely dependent on their caregivers as the complaint progresses. Thus, treatment aims to ameliorate the quality of life and drop complications. Pneumonia is a common cause of death, followed by suicide.[1]

ETIOLOGY

The complaint is inherited equivalently from the mother and father, more than 80% of those evolving symptoms before age 20 inherit the disfigurement from the father. Certain homozygotes for HD exhibit clinical characteristics similar to the aspect of HD heterozygotes, denoting that the unpretentious chromosome doesn't devaluate the condition symptomatically. An area close to the short arm of chromosome 4 contains a polymorphic (CAG), trinucleotide reprise that is remarkably expanded in all individualities with HD. The expansion of this trinucleotide reprise is the inheritable revision responsible for HD. The range of CAG reprise length in normal individualities is between 9 and 34 triplets, with a standard reprise length on normal chromosomes of 19. The reprise length in HD varies from 40 to over 100. Reprise length is identified equally with the age of onset of HD. The younger the age of onset, the more advanced the probability of a large reprise number. The medium by which the expanded trinucleotide reprise leads to HD's clinical and pathological features is unknown. The HD mutation lies within a large gene (10 kb) designated HTT (preliminarily

IT15) that encodes huntingtin, a protein of about 348,000 Da. The trinucleotide reprise, which encodes the amino acid glutamine, occurs at the 5' end of HTT.[2]

PATHOPHYSIOLOGY

HD is depicted by pronounced neuronal misplacement in the brain's striatum (caudate/ putamen). Atrophy of these edifices proceeds in an orderly manner, earliest affecting the tail of the caudate locus and also pacing antecedently from mediodorsal to VL. Interneurons and sensational outstations are spared mainly, whereas the striatal protuberance neurons (the medium spiny neurons) are oppressively affected. This leads to large diminishments in striatal GABA attention, whereas somatostatin and DA levels are relatively saved.

Selective vulnerability also appears to underlie the development of chorea. In most adult-onset cases, the medium spiny neurons that project to the GPi and SNpr (the indirect pathway) appear to be affected earlier than those projecting to the GPe (the direct pathway). The disproportionate impairment of the indirect pathway increases the excitatory drive to the neocortex, producing involuntary choreiform movements. In some individuals, rigidity rather than chorea is the predominant clinical feature; this is especially common in juvenile-onset.[3]

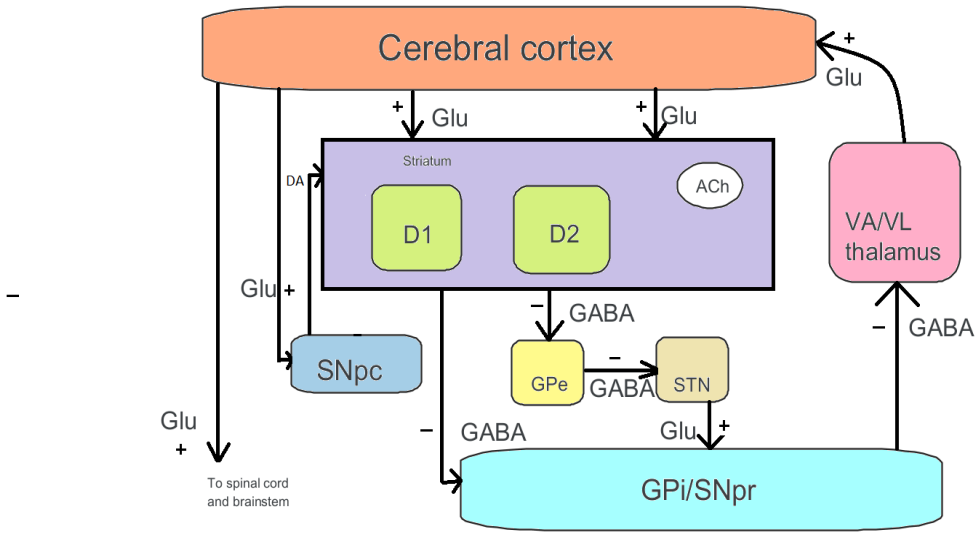


Figure No. 1: The basal ganglia in Huntington disease

PHYSICAL SYMPTOMS

The disease is liable to affect patients between the ages of 30 to 50. The signs and symptoms usually include motor, cognitive, and psychiatric disturbances. Rarely can show weight loss, sleep disturbances, and dysfunction of the ANS.

Motor Disturbances:

These involve the distinctive unintended moves which originally commence in the distal circumstances and are of a lower degree but could go on to affect the facial muscles as well. The movements also spread gradationally to the further proximal and axial muscles and are of lesser breadth. Motor symptoms tend to be progressive. Beforehand in the disease, they are substantially hyperactive with involuntary chorea. In the after stages, still, hypokinesia with bradykinesia and dystonia predominate. Dysarthria and dysphagia develop during the disease, which could lead to aspiration in some cases, with pneumonia being a common cause of death. Dystonia, characterized by increased muscle tone with slower movements, leads to abnormal posturing similar to torticollis and can be the first sign of motor involvement in HD. The motor disturbance in diurnal conditioning progresses over time and can lead to difficulties in walking, standing and frequent falls.[5]

Behavioral and Psychiatric Symptoms:

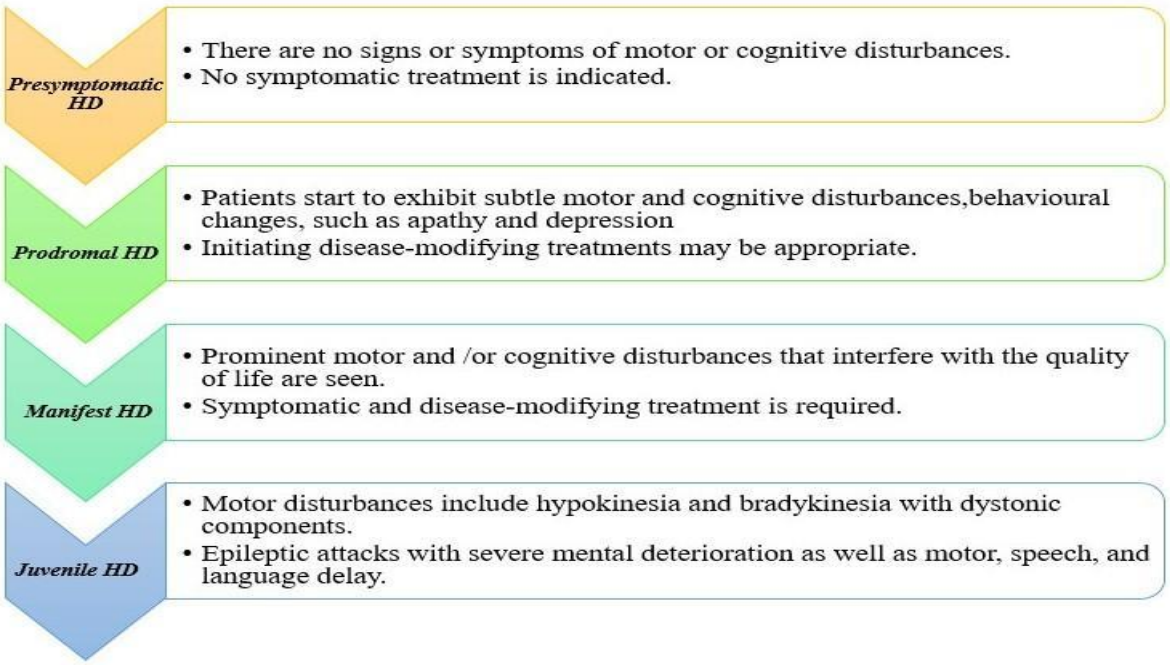
Behavioral and Psychiatric symptoms are oftentimes compatible with anterior lobe dysfunction. Primarily, patients may present out of attention, impulsivity, and perversity. The perversity is much more severe and leads to outbursts of angriness and aggression. Afterward on in the disease, there is an emotional weakness with noticeable apathy, loss of suspicion, and creativity. The anterior lobe symptoms are probably due to front striatal degeneration. The most common criterion of the disease is apathy, which is progressive and manifests alongside progressive motor disturbances and cognitive decline. Depression is also generally reported, but it is unclear whether these are due to the incorporation of the condition or upholding neural pathology. This includes a lack of knowledge of all three specialties of the disease (motor, cognitive, and psychiatric).[4,5]

Cognitive Disturbances:

The cognitive inconstancies are furthermore conspicuous for executive connections with patients having difficulty organizing, multitasking, and planning. These symptoms also progress with other cognitive deficiencies steering to dementia. Dementia in HD is subcortical, and memory loss originates from an ineffective search of memory more readily than a deficient memory, and features similar to apraxia and aphasia, which is usual in cortical dementia are scanted in HD. Psychomotor proceedings go oppressively decelerated.[5]

Other secondary symptoms include Ataxia, Gait abnormalities, abnormal eye movement, and Seizures.

Clinical Course and Classification [6]



Diagnosis

Therapeutic clinical trials direct to estimate the effectiveness of implicit disease-qualifying treatments during pre-manifest HD, which need biomarkers to serve as outgrowth measures. Competent ‘pharmacological’ or ‘efficacy’ biomarkers are those that reliably and objectively predictably react to treatment. Some efficacy biomarkers may also serve as ‘state biomarkers’ or ‘biomarkers of consecution,’ employed as intimations of condition inflexibility. All

biomarkers should be accessible, effortlessly accessible, unaffected by comorbidities, and possess limited variability amongst the ordinary population.[7][8]

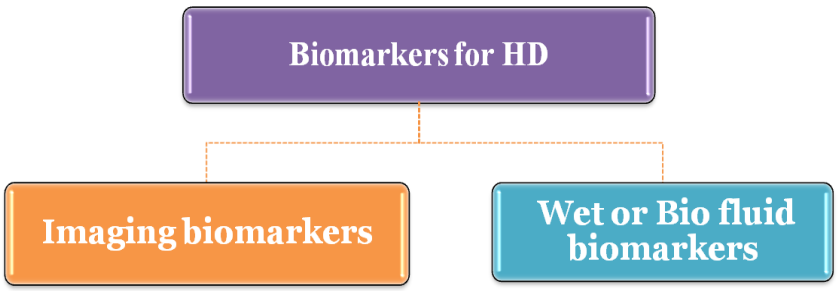
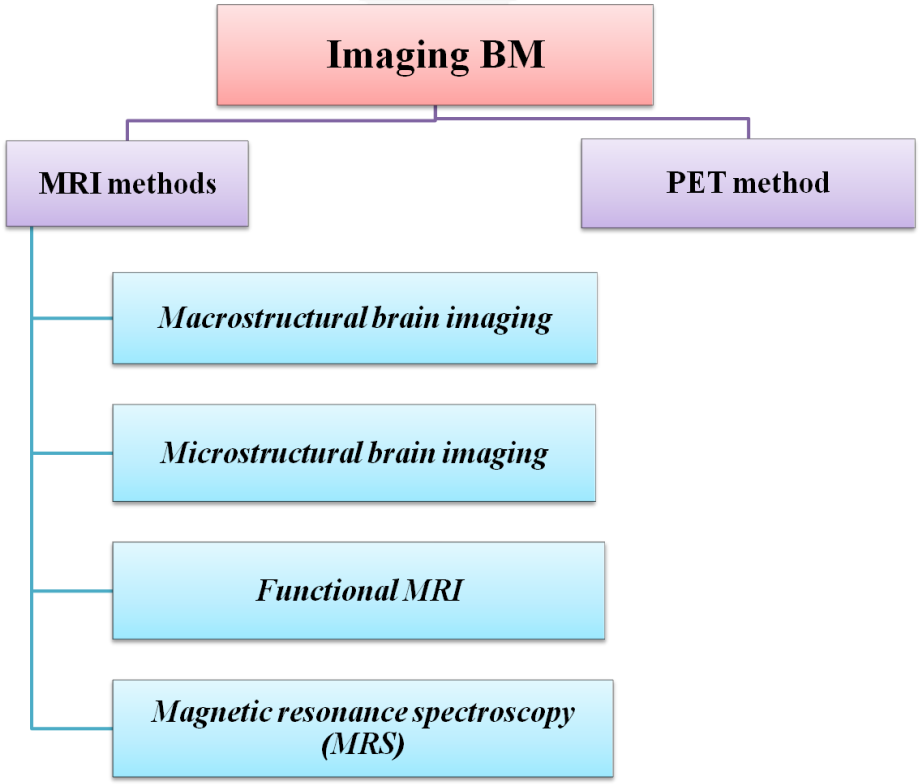


Figure No. 2: Classification of Biomarkers

Imaging Biomarkers

Structural imaging has shown its utility in monitoring disease progression in the incredibly early pre-manifest stage. Volume loss, notably in the striatum, is detectable in 1-2 decades before the development of motor features. The atrophy progresses over time and correlates with the disease load.[9]



Macrostructural Brain Imaging

Large longitudinal studies (PREDICT-HD and TRACK-HD) have shown significantly faster rates of decline in striatal volume in premanifest and manifest HD individuals compared with age-matched controls, even in those individuals who are more than 15 years from the estimated onset of diagnosable signs. Inconstancies in subcortical structures can correspondingly be detected by employing shape analysis.[9,10]

PREDICT-HD	Regions Affected	Volumetric Loss
Pre-manifest HD	Striatal atrophy, cortical grey matter atrophy	White matter in frontal lobe
Manifest HD	Striatal atrophy	
TRACK-HD	Regions Affected	Volumetric Loss
Pre-manifest HD	Striatal atrophy within corpus callosum	White matter in frontal lobe
Manifest HD	Posterior white matter tracts	

Microstructural Brain Imaging

Diffusion tensor imaging (DTI) has revealed abnormalities in neuronal fiber orientation and integrity in white matter and subcortical grey matter structures in both premanifest and manifest HD. Abnormalities in the cortico-cortical fibers in the corpus callosum could result in cortical ‘disconnection’ effects. Other measures from DTI, including mean diffusivity, and radial and axial diffusivity, have also been found to be abnormal in HD.[9,10]

HD	Regions Affected	Volumetric Loss	Other Measures
Pre-manifest HD	Abnormalities in white matter, sub-cortical grey matter & reduced diffusivity in putamen	Demyelination in Corpus callosum	Increased anisotropy
Manifest HD		White matter corpus callosum	Abnormalities in mean, radial, and axial diffusivity

Functional MRI

Functional MRI (fMRI) incorporates blood oxygen level-dependent (BOLD) contrast, reflecting neuronal activity before structural brain damage.

Functional changes include regional overactivation and under activation which could be signs of dysfunction, compensatory overactivity, or both.

In premanifest HD, functional connectivity has been reported to be abnormal in the motor system and cognitive systems.[11]

Magnetic Resonance Spectroscopy (MRS) or Chemical MRI

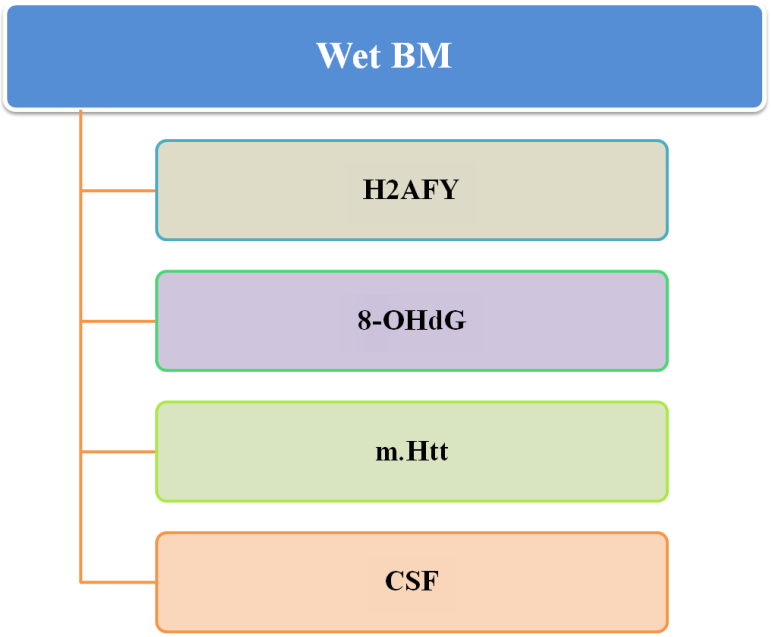
Magnetic Resonance Spectroscopy (MRS) has been used to identify alterations affecting N-acetyl aspartate (NAA), glutamate, and glutamine. Levels of myoinositol are elevated in the putamen of patients with early HD, correlating with motor dysfunction. Additional metabolites, such as lactate, glutathione, and γ-amino butyric acid, might increase the power for identification of physiological measures associated with early brain change in HD.[12]

PET Methods

Initial 18F-fluorodeoxyglucose (FDG)-PET studies in patients with HD showed glucose hypometabolism in the striatum, with a suggestion of possible hypermetabolism preceding the decrease. FDG-PET, in combination with network analysis tools, may identify specific patterns of abnormal brain function in the prodromal stages of HD.[13]

Wet or Biofluid Biomarkers

Wet Biomarkers, (those acquired from body fluids), are another implicit origin of applicable outgrowth measures, specifically, if they reflect the disease's pathobiology. Various pathologic mechanisms have been implicated in HD, yielding numerous potential molecular markers. [14]



H2AFY

The pathogenesis of HD has the dysregulation of gene transcription through post-translational modifications of histones. H2AFY is a particular histone that is elevated in individuals with HD, though it does not track disease progression. However, it has shown promise as a potential therapeutic marker. In subjects with early HD, H2AFY levels responded to treatment with Sodium Phenylbutyrate, a histone deacetylase (HDAC) inhibitor, which is known to suppress neurodegeneration in mouse models of HD.[15]

8-hydroxy-2-deoxyguanosine (8-OHdG)

8-hydroxy-2-deoxyguanosine (8-OHdG) is a measure of oxidative stress, which is believed to be involved in the pathogenesis of HD. Elevated 8-OHdG was detected in HD subjects' brains and blood in several studies, and levels correlated with closeness, to project the disease onset. In human HD studies, 8-OHdG levels also decreased following treatment with the antioxidants creatine27, and Coenzyme Q10 (CoQ), but they remained unchanged in a subsequent, pre-manifest trial of CoQ, refuting its reliability.[16]

Mutant Huntingtin Protein (mHtt)

It is the principal pathogenic molecule of HD. Direct quantification of the mutant huntingtin protein itself shows as a pathogenically relevant marker. Mutant huntingtin levels are observed to rise with disease consecution, owing to the accretion of N-terminal fractions. The concentration of mutant huntingtin correlates with both CAP score and brain atrophy rate,

indicating implicit functional applicability. In addition, besides being detected in CSF and blood, it is also measurable in saliva, providing convenient, non-invasive access to a protein whose damage is focused on the CNS.[17]

Cerebrospinal Fluid

Hypothesis-driven studies will focus on functional correlates and neurobiological underpinnings of detectable changes which are already reported, such as immune activation, transcriptional dysregulation, and cholesterol biosynthesis. Another possibility is to track striatal degeneration using CSF markers such as DARPP32 or TCIP2, which would be predicted to be released into the CSF by dyeing medium spiny neurons.[18]

Treatment / Management

There is no cure for HD. However, many therapeutic options exist for treating signs and symptoms to improve the quality of life. Treatment is primarily pharmacological as well as supportive. Numerous medicinal and surgical options have been estimated for their efficacy in decreasing chorea, taking in dopamine antagonists, benzodiazepines, acetyl cholinesterase, lithium, profound brain stimulation, and glutamate antagonists. These measures address the hyperactive movement complications associated with HD, suchlike as chorea, dystonia, and myoclonus. Additional remedies, as readily as behavioral plans, and cognitive interventions.[19,20]

Symptomatic Treatment	
Drugs	Tetrabenazine, Deutetrabenazine
Mechanism	Tetrabenazine, and the related drug reserpine are inhibitors of VMAT2 and cause presynaptic depletion of catecholamines. Tetrabenazine is a reversible inhibitor; inhibition by reserpine is irreversible and may lead to long-lasting effects.
Therapeutic use	For the treatment of chorea associated with HD.
Dose	125 mg daily
Metabolism	Tetrabenazine is extensively metabolized by CYP2D6.
Adverse effects	Both drugs may cause hypotension and depression with suicidality.
Contraindications	Concurrent or recent MAO inhibitor or reserpine.

Non-medical Interventions

Probative care with attention to diet, nursing, and special accouterments is commended. Smoking and alcohol usage is unnerved. Emotional prop-up, as well as consolation, can give comfort to patients residing with HD and their families.

Gene Therapy

The silencing of mutant genes provides an occasion for treatment. This could either repair function by restoring to normal neuronal ambits that are dysfunctional but not dead or could exist neuroprotective with an absence of incarnation of the disease. Quantitative measures of brain regions such as the striatum are good biomarkers for disease progression and are useful in the upcoming gene therapy studies.[21]

New Therapies under Investigation

Pharmacological agents that are being studied include inhibiting apoptosis, excitotoxicity, HTT aggregation, HTT proteolysis, phosphorylation, and oxidative damage. Compounds that modify transcription, mitochondrial, and chaperone activity are also being investigated.

Treatment options that have shown improvements in preclinical animal models and have advanced to clinical trials include the following: minocycline, memantine, sodium butyrate, and PDE10a inhibitor.

Experimental therapies include pridopidine, laquinimod, and a semaphorin-4D neutralizing antibody that is still in development.

Gene silencing to target the cause of HD is safe in preclinical animal studies. These are set to either silence all HTT expressions non-selectively or widely for the mutated HTT allele.

Cell transplantation has shown variable results and safety, as well as the efficacy of IV injecting in mesenchymal stem cells, is being tested. Recent studies indicate that the m- HTT gene can enter allografted neural tissue.[22]

The challenges in research discoveries for the treatment of Huntington's Disease [23]

1. The Cellular and Molecular Pathways to Be Targeted for HD Therapy Development are Still Unclear:

Many cellular and molecular pathways have been suggested to contribute to HD. These include a role of polyQ aggregates and misfolded mutant huntingtin (mHtt) in neurotoxicity; a role of a variety of mHtt fragments in the pathology; and a role of mHtt in mitochondrial dysfunctions, involving imbalanced fusion and/ or fission (similarly called mitochondrial dynamics), accelerated mitochondrial immobility in the neurons, repression of mitochondrial biogenesis, and dysregulated mitochondrial bioenergetics.

2. Lack of Optimal Animal Models to Test Therapeutic Approaches:

It is delicate to produce a befitting transgenic model for HD because of the size of the mutated gene, the discrepancy in the number of polyQ duplications between patients, and finding out that mHtt creates pathology in only named areas in the brain. Further, the slow progression, age dependency, and cognitive pathologies of the disease are difficult to recapitulate and assess in animal models.

3. The Challenge in Developing Clinical Trials

Some of the challenges in developing clinical trials for HD are typical for any clinical trials in patients with a rare disease: a limited number of patients, geographical challenge for patients to access trial sites, and the number of competing clinical trials for the same patient populations, etc. Another challenge related to the nature of HD is that it progresses over a prolonged period (years). There are differences in the severity and the rate of disease progression. The clinical assessment for HD is not sufficiently quantitative, objective, and robust and there are no surrogate markers to assess disease progression and therapeutic benefit over a short trial time.

4. Target to Be Chosen for HD Drug Development

Mutant huntingtin (mHtt) interacts with the mitochondrial fission machinery, specifically with dynamin-related protein 1(Drp1). This interaction impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in HD. Thereby we opted to focus on determining whether inhibition of excessive fission, by inhibiting excessive Drp1 activation, would reduce mHtt-induced pathology.

Lack of Biomarkers to Assist in Patient Assessments during Clinical Trials

So far only clinical examinations, which are not sensitive enough to detect slight changes over a brief period, are used to assess disease progression. Sensitive surrogate HD biomarkers will allow following the beneficial effect of a tested drug before the manifestation of clinical symptoms. Some biomarkers that have been suggested include plasma creatine kinase (CK-BB isozyme), whose levels are reduced in R6/2 mice and humans, other biomarkers include 8-hydroxy-2-deoxyguanosine (8-OH-2-dG) and H2AFY.

CONCLUSION

There are no disease-modifying treatments accessible for HD, but numerous are in progression. Various challenges are involved in its diagnosis, different biomarkers are used as indications of disease severity, and these biomarkers can be useful in the diagnosis of Huntington's disease. An objective biomarker denoting this time point would improve onset accuracy, and ideally be sufficiently sensitive to monitor progression leading up to this juncture. Clinical, cognitive, neuroimaging and biochemical biomarkers are being

investigated for their potential for clinical use and their value in the development of future treatments for patients with Huntington's disease. The persistent evolution of functional, neurochemical, and other biomarkers raises possibilities that these biomarkers might be applicable for coming trials of disease-qualifying curatives to delay the onset and decelerate the consecution of HD.

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