

REVIEW ON HUNTINGTON'S DISEASE

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ABSTRACT

Huntington disease (HD) is an uncommon neurodegenerative disorder of the central nervous system that is characterized by unwanted choreatic movements, behavioral and mental disorders, and dementia. In the Caucasian population, the estimated prevalence ranges from 1/10,000 to 1/20,000. The typical age range for the onset of symptoms is 30 to 50. Some people with juvenile Huntington's disease (JHD) experience behavioral issues and learning challenges at school before the age of 20. The typical symptom is chorea, which progressively affects every muscle. Every psychomotor function is significantly delayed. Patients experience cognitive decline and psychiatric problems.^[1] HD is an autosomal dominant hereditary disorder caused by the Huntingtin gene on the short arm of chromosome 4p16.3, which has an expanded CAG repeat (36 repeats or more). If the CAG repetition is longer, the illness begins earlier. The repetition often exceeds 55 when JHD occurs. When someone has a parent with HD, the diagnosis is made based on clinical signs and symptoms and is confirmed by DNA testing. Every psychomotor function is significantly delayed. Patients experience cognitive decline and psychiatric problems pre-manifest diagnosis should only be performed by multidisciplinary teams in healthy at-risk individuals who want to find out if they have the mutation. Differential diagnoses include other causes of chorea, such as general internal ailments or iatrogenic illnesses. Clinically recognized HD cases have phenocopies that do not have genetic mutation.^[2] Amniocentesis and chorionic villus collection can be used for prenatal diagnosis. In vitro fertilization is available in a number of nations for preimplantation diagnosis. No remedy is available. Treating symptoms in order to improve quality of life should be the foundation of interdisciplinary management. Dopamine

receptor depleting or blocking medications are used to treat chorea. Depression and violent conduct may require both non-medical care and medication. As the illness worsens, people become totally dependent on care, which eventually leads to their death. Suicide is the second most common cause of mortality, after pneumonia.^[3]

KEYWORDS

Huntington's disease; Caucasian; surpasses; iatrogenic illness; preimplantation; amniocentesis; mortality; phenocopies.

INTRODUCTION

A progressive neurological condition, Huntington's disease is inherited autosomally dominantly. It exhibits a distinctive phenotype that includes behavioral abnormalities, lack of coordination, gradual cognitive decline, and involuntary movements including chorea and dystonia. The illness can emerge at any age, from infancy to senescence, even tho symptoms typically start in mid-adulthood, frequently following reproduction.^[4]

An expansion of CAG trinucleotides repeats in the HTT gene underlies Huntington's disease by generating a pathogenic, mutant version of the multifunctional protein huntingtin. The mutant protein features an excessively long polyglutamine [polyQ] sequence corresponding to the CAG expansion; this abnormal protein exerts toxic effects that drive neuronal degeneration and death. Although medium spiny neurons in the striatum are particularly susceptible to mutant huntingtin, Huntington's disease is increasingly recognized as a systemic disorder affecting the entire brain and body.

The known genetic basis enables both predictive and diagnostic genetic testing.^[5]

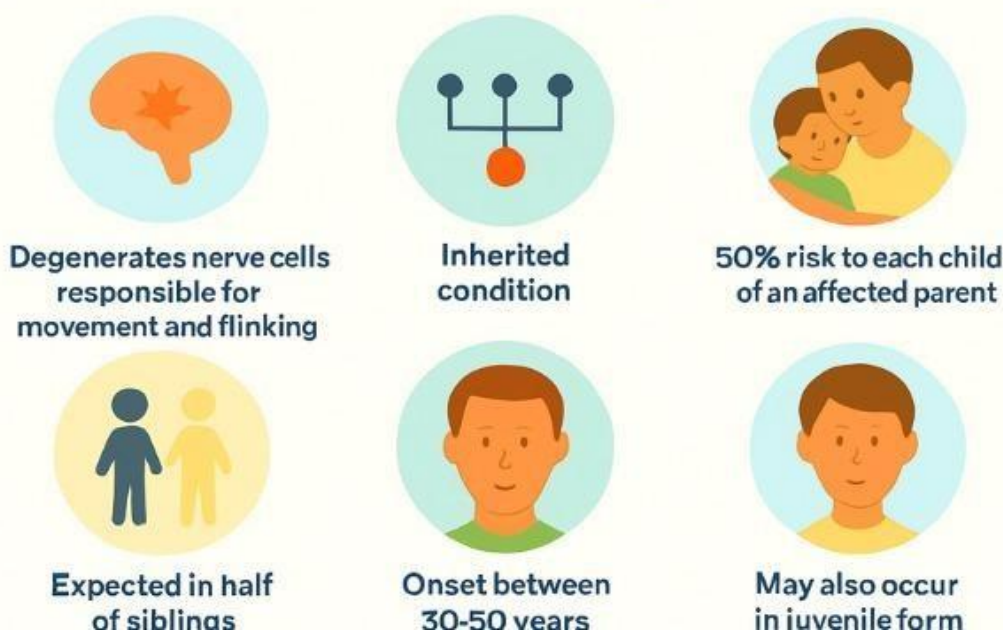
A young physician from Connecticut called George Huntington wrote one of the first descriptions of the disease that would bear his name in 1872 (Huntington 1872). One of only two magazines he produced during his career, it highlighted the families his father, a physician, was taking care of. The predominantly hereditary neurological disorder was characterized by excessive motor movements and neuropsychological deficits. Many people still consider George Huntington's to be the first substantially thorough description of Huntington's illness (HD), notwithstanding previous reports of a neurological ailment that is most certainly HD (Harper 2002; Lund 1860).^[6]

ETIOLOGY

HD is caused by an autosomal dominantly inherited CAG B trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4. This results in the production of a mutant huntingtin (mHTT) protein with a very long polyglutamine/repeat.^[7] Those having more over 39 CAG repeats are certain to develop the illness, while reduced penetrance is seen between 36 and 39 repeats.

It is expected that a father with a CAG repeat length in the intermediate range may give birth to a child with an increased pathogenic repeat length when the gene is passed down through the paternal line. Male sperm have larger repetition sizes and greater repeat diversity than somatic tissues, which explains this.^[8]

What to Know About Huntington's Disease



EPIDEMIOLOIGY

The prevalence of HD in Western populations ranges from 10.6 to 13.7 per 100,000. In Hong Kong, Taiwan, and Japan, HD is far less prevalent, with a prevalence of 1–7 per million. Black groups in South Africa had lower rates than mixed and white populations. Ethnic group differences in the prevalence of disease are associated with genetic polymorphisms in the HTT gene. In populations with a high incidence of 2, the average CAG repeats are longer. For example, individuals with European ancestry often score between 18.4 and 18.7, while those with Asian ancestry typically score between 16.9 and 17.4.^[9] Why do different groups

still have different huntingtin alleles? What is the genetic fragility of Huntington's disease? There hasn't been a noticeable increase or decrease in the number of children born to those impacted.^{4; 94} Additionally, other than a potential decreased risk of cancer, which may be connected to an overexpression of TP53 in Huntington's disease, the HD gene does not appear to provide any prospective health benefits.¹⁹⁷ Expanded huntingtin alleles do not appear to offer any protection against infectious disease epidemics.^[10]

GENETICS

Restriction-fragment polymorphisms were used to map one of the first loci associated with the disease.^[11] was the locus for HD. This finding enabled the presymptomatic identification of HD-allele carriers and revealed that HD is a true dominant disorder with homozygotes presenting a clinical phenotype identical to heterozygotes.^[12,13] Despite this early success, it took around ten years of work to identify the HD gene. As a reward for the investigators' persistence, the locus implicated was discovered in 1993.^[14]

HD GENE AND GENETIC MODIFIERS

Many of the genetic characteristics of the disorder, such as the variation in age at onset, the propensity for juvenile disease to be inherited from fathers, and the sporadic emergence of new HD mutations, are explained by the nature of the genetic flaw in the HD gene.^[15] The disease is brought on by a genetic mutation that increases the number of repeats of three nucleic acids (C, A, and G) in the coding region of the HD gene's first exon.^[17] The gene is found on chromosome 4p16.3.^[16] This CAG "triplet" is typically repeated 20 times, but the sickness manifests when the number of repeats roughly doubles to 40 or more.^[17, 18] There have been reports of significant familial aggregation for the age at which HD first appears.^[19] It was shown that pairs of affected siblings had almost comparable onset ages regardless of the magnitude of the HD repeat mutation using onset ages adjusted for the mutation. After accounting for repetition size, estimates of the heritability of onset age vary from 56% to 65%.^[19] Thus, modifier genes account for 56% to 65% of the variation in onset age that cannot be explained by repetition size. Djousse et al. discovered that the size of the normal repeat had an impact on onset age in addition to family aggregation. In contrast to the HD repeat itself, it is noteworthy that larger normal repeats are linked to later onset, even though the effect is tiny and barely explains 1% of the variation in onset age. A genome scan to find genes that might affect HD expression was prompted by the repeat-adjusted onset age's high heritability.^[20]

MOLECULAR PATHOGENESIS

The mHTT causes neuronal dysfunction and death in a number of ways. These include the direct effects of the exon 1 mHTT fragment, the propensity of mHTT to form aberrant aggregates, and its effects on transcription, translation, axonal transport, cellular proteostasis, mitochondrial, and synaptic function.^[21,22] Particularly vulnerable to the effects of mHTT are striatal medium spiny neurons (MSNs). A hyperkinetic phenotype results from the initial loss of MSNs of the indirect pathway, whereas a hypokinetic phenotype follows the loss of MSNs of the direct pathway.^[22] The course of striatal illness is biphasic. It is unclear why indirect pathway MSNs are selectively vulnerable. However, the pathophysiology of HD has been connected to dopamine D2 receptors, which are expressed by indirect but not direct MSNs. Additional theories include the toxicity of repeat-associated non-ATG (RAN) translation proteins, glutamate excitotoxicity from cortico-striatal connections, and loss of brain-derived neurotrophic factor.^[23, 24]

MACROSCOPIC PATHOLOGY

Post-mortem examinations reveal diffuse atrophy of the caudate and putamen with degeneration along a caudo-rostral, dorso-ventral, and medio-lateral gradient. The globus pallidus and nucleus accumbens are also affected, albeit less so.^[25]

Five grades make up the classification scheme for HD pathology.

Grade 0: no gross or microscopic abnormalities that could be associated with HD, but clinical evidence for HD.

Grade 1: Moderate fibrillary astrocytosis at the microscopic level but no macroscopic abnormalities in the putamen or caudate

Grade 2: There are no macroscopic alterations in the Globus Pallidus but macroscopic changes in the caudate and putamen.

Grade 3: lateral segment of the globus pallidus showing fibrillary astrocytosis with the medial segment of the GP unchanged.

Grade 4: Shrunken caudate yellowbrown in colour, widened anterior horn of lateral ventricle and smaller nucleus accumbens^[26]

Other brain regions, including as the thalamus, sub-thalamic nucleus, white matter, and cerebellum, also show changes at grades 3 and 4. Even in stages 3 and 4, cerebral Neurol. cortical atrophy varies.^[26]

These early pathological results, especially loss of caudate and putamen grey matter volume and loss of both striatal and cortical white matter, have recently been verified in vivo by advancements in magnetic resonance imaging (MRI).^[27]

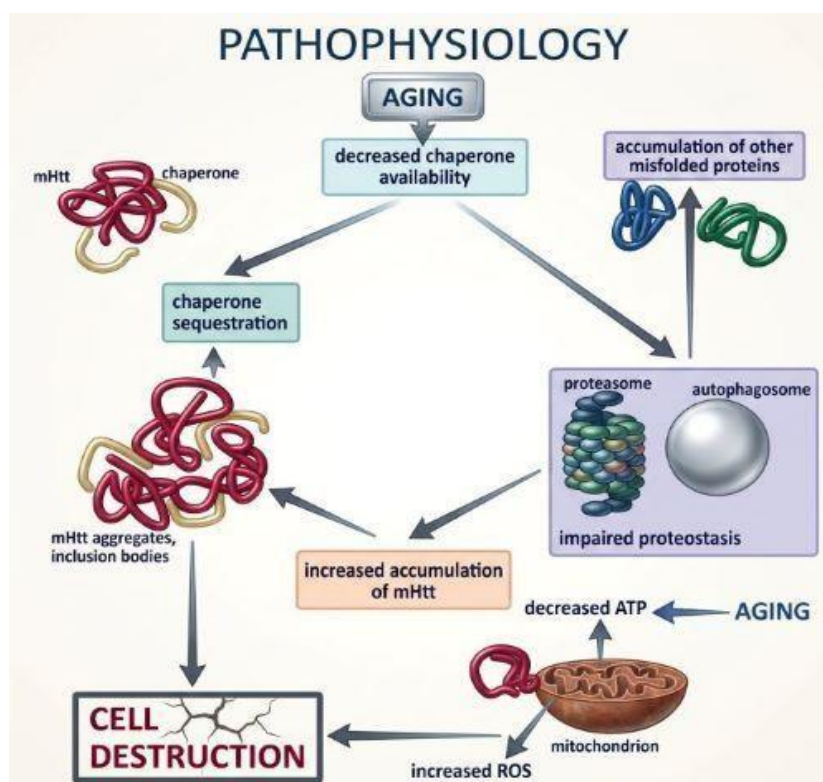
PATHOPHYSIOLOGY

HTT is located on chromosome 4p16.3 and codes for the protein huntingtin⁵, whose normal function is unknown. Near the N-terminus of huntingtin is a variable-length polyQ region. Whether a person is at risk, normal, or has been clinically diagnosed with Huntington's disease, the length of the CAG trinucleotide repeat that encodes this region can be ascertained using a simple polymerase chain amplification assay employing certain flanking oligonucleotide primers.^[28] In the normal population, the repeat is polymorphic, spanning from 6 to 35 units; when it expands to ≥ 40 units, the mutation becomes highly penetrant, starting a disease process that eventually leads to the appearance of diagnostic motor symptoms. Because some individuals with repeats of 36–39 CAG units have Huntington's disease while others have normal life spans without a diagnosis, these repeats show reduced penetrance. The middle CAG repeat region (27–35 units) is where meiotic transmission first creates instability in the CAG repeat; as CAG length grows, the frequency of this instability increases. Although it seldom shows a significantly larger increase, the repetition's length can vary by one to several CAGs, with increases predominating. Some males may have a particular tendency to CAG repeat instability during spermatogenesis, while the latter occurrences are almost always restricted to transmission from dads.^[29]

Numerous genotype-phenotype investigations in populations with Huntington's disease have established criteria for the mechanism that initiates pathogenesis and have suggested that pathogenesis is modifiable.^[30]

The length of the CAG repeat in HTT is the primary determinant regulating the rate of pathogenesis that leads to the characteristic motor symptoms that support the clinical diagnosis, in addition to deciding whether an individual will develop Huntington's disease.^[31, 32, 33, 34, 35, 36, and 37] Importantly, the second HTT allele, whether normal or not, has no effect on the rate of the pathogenetic process that leads to clinical diagnosis; instead, the allele with the longer CAG repeat defines the date of start for these motor symptoms in a fully dominant manner.^[34] The length of the CAG repeat correlates with measurements in certain cellular assays (such as cellular energy charge [ATP:ADP ratio³¹] or cellular adhesion³² assays), suggesting that it may involve a gain-of-function that acts thru augmentation or dysregulation

of one or more normal functions of huntingtin, even though the precise nature of the pathogenetic trigger that meets these genetically defined criteria (CAG length-dependence, allele dose independence) is unknown.^[38,39] In any event, the molecular and functional repercussions of the CAG expansion can be shown in human mutation-carriers' cultured cells^[40] and in those individuals themselves, at least 15 years before Huntington's disease begins.^[41]



Clinical summary

Mental, cognitive, and motor impairments are the hallmarks of Huntington's disease (HD). Other less well-known but commonly incapacitating symptoms of HD include autonomic nervous system dysfunction, sleep and circadian rhythm problems, and unintentional weight loss. The average age of onset is between 30 and 50 years old, however the range is 2 to 85 years old. The usual duration of the condition is 17–20 years. Daily dependency grows as the sickness worsens and eventually leads to death. After pneumonia, suicide is the second most frequent cause of death.^[42]

Motor symptoms

Speech and feeding issues become increasingly noticeable as the illness deteriorates. These individuals therefore have a tendency to move slowly and struggle to start their movements. The degree of hypokinesia and chorea varies from person to person. The two extremes are the

young patient with overpowering stiffness and the very old patient who has been unwell for a long time and is likewise seriously affected in the final stages of the illness, bedridden with stiffness and flexion contractures in the limbs. Sluggish motions and elevated muscle tone are hallmarks of dystonia, which can lead to aberrant alignments such torticollis and trunk or extremity rotation. The initial motor symptom of Huntington's illness could be dystonia.^[43]

Psychiatric symptoms

Guilt, anxiety, and low self-esteem are prevalent. Unlike depression and anxiety, indifference is associated with the disease's stage. Suicide is more common in both early symptomatic patients and premanifest gene carriers. The period when independence wanes and the time of the gene test are when suicide risk is at its maximum.

Furthermore, worry is prevalent (34–61%), occasionally in conjunction with uncertainty regarding the beginning and/or course of the illness. In addition to interfering with the patient's life, compulsions and obsessions can make people angry and irritated. In retrospect, irritation is often the first sign, although it occurs throughout the entire course of the illness.^[43]

COGNITIVE SYMPTOMS

The sub-cortical pattern of cognitive disruption, which includes decreased emotion identification, processing speed, visuospatial ability, and executive function, can be observed years before symptoms appear.^[44]

The Stroop word reading test, which assesses executive function, the indirect circle tracing test, which assesses visuospatial performance, the emotion recognition test, and the symbol digit modalities test, which assesses psychomotor speed, can demonstrate longitudinal changes in early manifest disease over a 12- and 24-month period.^[13, 32] For those who are the furthest from the disease's beginning, stroop word reading has the most sensitivity, and this extends to premanifest HD at 36 months.

DIAGNOSIS

The diagnosis of HD is based on a confirmed family history or a positive genetic test, as well as the onset of motor disruption as assessed by the Unified HD rating scale (UHDRS) total motor score (TMS) diagnostic confidence score. Motor onset or "manifest" HD is indicated by a score of 4. The score goes from 0 (no motor abnormalities suggestive of HD) to 4 ($\geq 99\%$ to be associated to HD).

However, modest motor, cognitive, and six psychological impairments can be found up to ten to fifteen years before the onset of apparent disease; this is referred to as the premanifest stage of the disease.^[45]

Differential Diagnosis:

When chorea is the most obvious and presenting symptom, taking a history is the first and most crucial step. The usual differential diagnosis for motor sign chorea is listed in Table 1. The underlying cause is frequently an iatrogenic illness or another general internal disorder. There are very few genetically specific diseases that induce choreatic disorders. In about 1% of cases where the doctor has established a clinical diagnosis, the genetic test does not confirm HD. We call these phenocopies.^[46] Phenocopies are defined as a clinical diagnosis of HD with chorea, mental and/or cognitive symptoms, and an autosomal dominant mode of inheritance or family history.

Table 1: Differential Diagnosis for chorea

Hereditary :	- Huntington's disease - Wilson disease - Neuroacanthocytosis - dentatoRubroPallidoLuysian Atrophy (DRPLA), - benign hereditary chorea
Rheumatic conditions:	- chorea gravidarum - Sydenham chorea
Drug-induced :	- Neuroleptic medications - OralAnticonceptive medications - Cocaine - Levo-dopa, - phenytoine
Systemic disorders :	- Systemic lupus erythematodes (SLE) - AIDS - Hyperglycemia - Polycythemia Vera

Genetic counseling:

When the gene was discovered on chromosome 4 in 1983, linkage analysis enabled premanifest diagnosis for the first time.^[47] Linkage analysis results were given to the applicant, initially with a 93% certainty and then with a 98% certainty. Since the discovery of the CAG repeat on chromosome 4 in 1993, individuals at risk for HD may be diagnosed as true premanifest. It was the first ailment for which this approach was practically useful, providing an example of how to deal with new problems and difficulties. A manifesto was developed by the HD community, which is made up of doctors, scientists, and laypeople.^[48]

Step 1 involved consultation with a clinical geneticist, ideally in conjunction with a psychologist and a neurologist. Four to six weeks later, there is a second session (step 2) where blood is drawn. Six to eight weeks later, a consultation (step 3) with disclosure is planned. The procedure's exclusion criteria include being under eighteen, having a major mental illness, and being under external pressure. Long discussions focused on applicants who had a 25% risk at the time of the request. The protocol was modified to compel the applicant to make every effort to receive a result from the parent who has a 50% chance of HD. It is now possible for the candidate who is 25% at risk to take his exam.^[49]

Table 2: Huntington's disease phenocopy (OMIM)^[32]

	Mutation	Lucus
1. HDL1	octapeptiderepeat expansion <i>PRNP</i> gen	20pter.p 12
2. HDL2	CTG/CAG-expansion <i>JPH3</i> -gen	16q24.3
3. HDL3	Unknown	4p15.34
4. HDL4	TBP-gen CAG/CAA expansion	6q27
5. SCA1/2/3	ATXN1/2/3-gen CAG-expansion	6p23, 12q24, 14q24-q31
6. DRPLA	CAG-expansion <i>ATN1</i> -gen	12p13
7. Chorea-acanthocytosis	mutation <i>VPS13A</i> -gen	9q
8. McLeod syndrome	mutation <i>XK</i> -gen	Xp21.2-21.1
9. NBIA2	mutation <i>PLA2G6</i> -gen	22q13.1
10. NBIA1/PKAN	mutation <i>PANK2</i> -gen	20p13-12.3

Huntington disease-like is denoted by HDL, spinocerebellar ataxia by SCA, dentate Rubro Pallido Luysian atrophy by DRPLA, neurodegeneration with iron accumulation in the brain by NBIA, and pantothenate-kinase-associated neurodegeneration by PKAN.^[50]

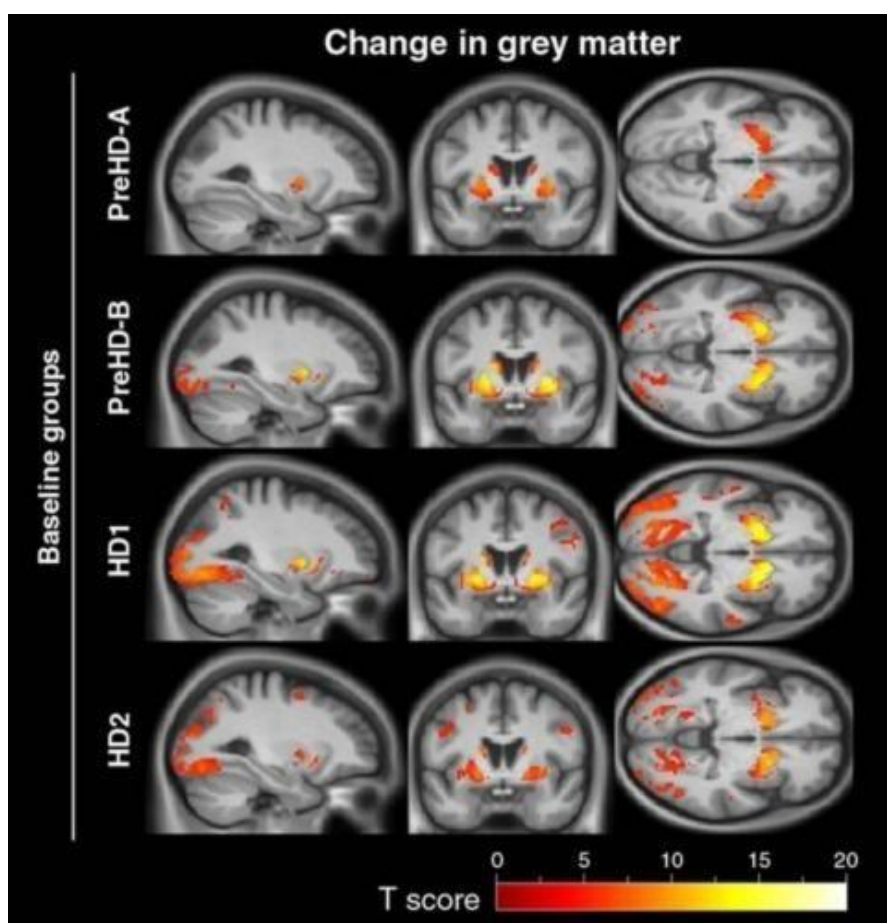
Disease progression and Phases in Huntington's disease

Preclinical phase

1. 50% at-risk stage, one impacted parent: future anxiety, Uncertainty regarding carrier ship, Taking care of the impacted parent
2. Gene carrier, premanifest stage: Carrier confidence 'A new role within the family, A renewed lack of certainty regarding onset, Taking care of one's own family and impacted parents
3. Transition phase: Strong emotions over cognitive changes, Behavioral shifts, Modifications to motor activity, there still uncertainty

Clinical phase

1. Clinical stage I: Neurological, cognitive, or psychiatric first symptoms, Chorea's most noticeable symptom, the primary psychological burden on the family Rarely, unless it's suicide
2. Clinical stage II: Suicide, euthanasia, and death by OT18; more extensive motor disruption; the beginning of physical dependence; the psychological and physical toll on the family.
3. Clinical stage III: Severe generalized motor disturbance, Nearly total bodily reliance The patient is entirely reliant on treatment. The family's primary physical burde and death.



Disease progression

The onset of symptoms often occurs between the ages of 30 and 50. Each person has a different rate of advancement. Over time, mental, motor, and cognitive symptoms get worse. After the onset of symptoms, the typical survival is between 15 and 20 years. Complications including aspiration pneumonia, infections, falls, or malnourishment frequently lead to mortality.^[51]

MANAGEMENT

Huntington's disease is now mostly managed by treating its symptoms because there isn't a viable disease-modifying drug. A group of medical experts (Box 1) who can handle the patient's wide-ranging effects on the person and family is part of ideal patient management. In fact, the European Huntington's Disease Network Standards of Care group issued management guidelines for dentists, physiotherapists, occupational therapists, nutritionists, and speech pathologists. It has also been emphasized how important Huntington's nurses are in providing care for patients and their families.^[52] Tetrabenazine, a synaptic vesicular amine transporter inhibitor that was approved in 2008 for the treatment of chorea¹³⁸, is the only medication that the FDA has expressly licensed for use in people with Huntington's disease. Other possible treatments for chorea in Huntington's disease patients include a deuterated tetrabenazine molecule and pallidal deep-brain stimulation.^[53] It has been noted in a number of papers that there is insufficient evidence to support any other pharmacological treatment for Huntington's disease. Based on surveys of Huntington's experts, a worldwide team produced a series of algorithms for the treatment of chorea, irritability, and obsessive-compulsive behaviors in 2011 in an attempt to lessen therapeutic nihilism in the lack of validated treatments. It is important to take the stance that drugs that help people with neuropsychiatric symptoms who do not have Huntington's disease should also be expected to treat those with Huntington's disease who have the same symptoms until further data is gathered.^[54]

RECENT ADVANCES AND EMERGENCY THERAPIES

DNA AND RNA TARGETING THERAPY

Perhaps the most promising approaches to changing the problem are the novel therapies that target the DNA or RNA of the mHTT gene to lower mHTT levels.

RNA can be targeted by small molecule splicing inhibitors, RNA interference (RNAi), or anti-sense oligonucleotides (ASOs). A first-in-human phase 1b/2a research is presently testing ASOs.^[55] They are administered intrathecally and catalyze RNase H's breakdown of HTT mRNA, which lowers the amount of mHTT protein produced. This causes a prolonged decrease in HTT mRNA levels of up to 80% in animal studies.^[56]

In RNAi-based methods, argonaute 2, the RNase enzyme found in the RNA-induced silencing complex (RISC), removes mRNA when RNA molecules attach to it in the cytoplasm.^[57]

Preclinical research is now being done on therapeutic approaches that use this methodology. Compared to ASOs, RNAi administration is more intrusive and necessitates intracranial injection into the striatum. However, HTT may be permanently reduced with a single treatment. In animal models of minor muscle atrophy.^[58] small molecule splicing modifiers have demonstrated promise, and screening for mHTT small molecule splicing modulators is presently in progress.^[59]

Zinc finger proteins and the CRISPR/Cas9 (clustered inter-spaced short palindromic repeats) system are two methods for targeting the DNA of mHTT. Zinc fingers are proteins that bind to DNA to form a structural motif. Synthetic zinc finger transcription factors that target CAG have been shown to reduce mHTT protein levels in animal models. However, since they produce foreign proteins, they may trigger immunological responses, therefore more research is required.^[60]

Recently, the CRISPR/Cas9 system—which bacteria utilize as a defense mechanism to cut foreign DNA—was modified for genome editing, opening up a number of potential applicable in the treatment of human diseases. Using this technique, the transcription start site, promoter regions, and enlarged CAG mutation of the mHTT gene were eliminated from the fibroblasts of a patient with Huntington's disease (HD). The mutant allele of the mHTT gene was permanently and specifically rendered inactive using this method.^[61] The potential of this approach was demonstrated by a recent study that successfully assessed it in a rodent model of HD; however, substantial preclinical research is still needed to bring these quickly developing technologies into clinical practice, especially in light of growing concerns about unintentional off-target mutations linked to CRISPR-Cas9 gene editing.^[62,63]

GENE THERAPY

The idea that adding genetic material to diseased cells could restore function has recently sparked a renewed interest in gene therapy. When a single gene deficiency predicts a disease phenotype that can be addressed by introducing the wild-type (wt) gene, gene therapy appears promising for a number of uncommon metabolic illnesses. However, genetic therapy for brain-related neurodegenerative diseases (NDs) present additional difficulties. such as (i) symptoms that frequently impact particular brain activities and pathways, requiring targeted gene delivery to specific neuronal or glial subtypes; (ii) widespread degenerative processes suggesting that more global vector delivery will probably be required for long-term effective treatment; and (iii) late onset of disease symptoms in which there has already

been substantial loss of neurons and injury to nonneuronal cell types, such as glia. The intricate and poorly understood genetic basis of several prevalent NDs, including Parkinson's disease, makes early identification of those at risk difficult, even though early illness discovery would allow management before clinical symptoms arise.^[64, 65]

Stem cell therapy

Human pluripotent stem cells (hPSCs), either as induced pluripotent stem cells (hiPSCs) or embryonic stem cells (hESCs), have attracted attention for neural replacement therapy. Before being transplanted, hPSCs are transformed into human neural stem cells (hNSCs) to reduce the risk of malignancy and enhance lineage specificity. Although early study indicated that hESC-derived NSCs may survive and generate new neurons in the QA lesion animal model of HD, transplanted hNSCs did not develop into region-specific neurons expressing markers of MSNs.^[66,67] Interestingly, Song et al.^[68] also discovered that hNSC transplantation alleviated the motor function deficit brought on by QA in the absence of MSN production. Unfortunately, this was not investigated in this study, although it is probably because neuroprotective factors were expressed by the transplanted hNSCs.

Several researchers used a variety of different procedures to differentiate hESCs into striatal precursors or lateral ganglionic eminence progenitors in order to promote differentiation into MSNs and boost lineage specificity.^[69,70] The production of MSNs upon transplantation into the QA-lesioned striatum was reported in all of these studies, indicating the necessity of driving hESCs to a lineage-specific progenitor fate prior to transplant. Only two of these investigations, however, looked at functional outcome; Delli Carri et al.'s study^[69] found a decrease in apomorphine rotations caused by QA lesions starting three weeks after transplant. Transplantation had no effect on apomorphine-induced rotations, according to the study of Arber et al.^[70] When comparing the two studies, this discrepancy in functional outcome could point to discrepancies in the differentiation protocol or differences within the transplanted cells age.

Additionally, there are more rigorous motor function tests, such as the cylinder, staircase, or corridor tests, that would offer a more accurate evaluation of functional result than the apomorphine-induced rotation test.^[71,72] Therefore, more thorough research is required to accurately evaluate the functional outcome, even though human ESC-derived NSCs may offer a potential cell source for HD cell replacement therapy. Additionally, the utilization of hESC-derived NSCs will be subject to ethical considerations about their therapeutic usage, just as fetal tissue.

COMPLICATIONS

Dysphagia:

Dysphagia in HD 65 Any anomaly in the passage of a bolus from the mouth to the stomach is referred to as dysphagia, and it can be classified as either oral, pharyngeal, or esophageal. Odynophagia (pain during swallowing), difficulty chewing solid textures, coughing, choking, or aspiration (ingested material passing below the vocal folds pre, during, or after pharyngeal swallow initiation) are some of the symptoms of dysphagia.^[73]

Psychiatric complications

The most prevalent mental illness that can coexist with HD is depression.^[74] Furthermore, depression has the greatest effect on systemic energy homeostasis.^[75] Numerous neuroendocrine changes and decreased appetite brought on by depression may result in a gradual loss of weight.^[75] Therefore, appropriate therapy for depression may have a positive impact on body weight. For depression in HD, standard psychiatric therapies are successful.^[74]

Malnutrition and weight loss

In 8, 10, and 12-week-old R6/2 and WT mice, correlations between body weight and malabsorption (measured as the percentage of food expelled as feces) were evaluated. At 12 weeks of age, the percentage of food evacuated as feces and body weight in R6/2 mice showed a statistically significant inverse association. Put another way, the mice lost more weight the more nutrients they were unable to absorb. The amount of food absorbed and body weight in WT animals did not correlate at any time point.^[76]

Upcoming projects

The best line of action might be to treat Huntington's disease while it is still asymptomatic. Numerous observational studies of at-risk individuals are currently investigating the feasibility of using the appearance of the clinical Huntington's disease phenotype or other disease biomarkers (such as changes on imaging examinations) as a potential endpoint for future clinical trials. Successes in animal models, the discovery of possible surrogate markers, improvements in symptomatic medication, and the development of efficient study designs are all tangible causes for optimism in the Huntington's disease community. With enough funding for continued research, the creation of a helpful treatment seems feasible.^[77,78]

CONCLUSION

Huntington's disease is a terrible, progressive hereditary neurological condition that impairs mental, cognitive, and physical abilities, resulting in severe impairment and a lower quality of life. Despite the fact that there is now no established cure and that therapy is still mostly symptomatic, our understanding has greatly advanced breakthroughs in molecular genetics, enabling early diagnosis, genetic counseling, and predictive testing. In order to improve patient outcomes and quality of life, multidisciplinary care involving neurologists, psychiatrists, physiotherapists, speech therapists, dietitians, and genetic counselors is essential. Gene therapy, RNA-targeting techniques, CRISPR-based gene editing, and stem cell therapy are examples of emerging therapeutic options that provide significant prospects for disease modification and could revolutionize Huntington's disease management in the future. To create safe and efficient treatments that can slow the advancement of the disease and eventually enhance the lives of afflicted people and their families, more research, early intervention, and cooperative clinical efforts are crucial.

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