HUNTINGTON’S DISEASE-A NEURODEGENERATIVE DISORDER

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ABSTRACT

Huntington’s disease (HD) is a devastating neurodegenerative & genetic disorder that occurs in patients with a mutation in a sequence of human DNA that is known as the HD gene, huntingtin gene & also expansion of ht gene on chromosome 4 which encodes for huntingtin gene. It is inherited as an autosomal dominant trait. This means that an individual only needs to receive one copy of the HD gene from an affected parent to express the disorder. Therefore, if one parent expresses the disorder, their offspring have a 50% chance of inheriting it. Patients are affected by early cognitive signs, motor deficits, and psychiatric disturbances. It is of two types i.e. adult & juvenile Huntington. According to severity HD can be divided in 3 stages. A significant increase in the activity of this enzyme in both the caudate nucleus and putamen is observed with this disease. The resistance of these neurons suggests that the gene defect in Huntington's disease may be modifiable by the local biochemical environment. Symptoms are attributed to cell death in the striatum and disruption of cortical-striate circuitry. Mechanisms of cell death are unclear, but processes involving mitochondrial abnormalities, excitotoxicity, and abnormal protein degradation have been implicated. Many factors likely contribute to neuron death and dysfunction, and this has made it difficult to systematically address the pathology in HD. The Huntington's disease gene, was the first autosomal defect mapped using only DNA markers. Pharmaceutical therapies are commonly used in patients to treat disease symptoms. These have limited benefit. Several neuroprotective therapies are being evaluated in animal models.

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of HD as well as in clinical trials. Similarly, cell replacement strategies such as fatal transplantation have been used in the clinic with minimal success, making future cell replacement strategies such as stemcell therapy uncertain.

**Keywords:** Huntington’s disease, Huntingtin gene, CAG, Neurodegenerative, Autosomal.

**INTRODUCTION**

Huntington disease is an inherited neurodegenerative disorder caused by a gene defect on chromosome 4 that causes selective loss of neurons, particularly in the striatum. The gain of function mutation involves an expanded CAG trinucleotide repeat that produces a long tract of consecutive glutamine residues in huntingtin, a large protein of unknown function. (1) The first description by Waters, of a patient with what we now call Huntington’s chorea, dates from 1842. But it was not until 1872, after the lecture and description of the disease by George Huntington, that it became known as Huntington’s chorea. It passes within families from generation to generation with onset in middle age and characterized by unwanted choreatic movements, behavioural and psychiatric disturbances and dementia. For many decades its name remained unchanged, until the nineteen-eighties when, fully aware of the extensive non-motor symptoms and signs, the name was changed to Huntington’s disease (HD). In 1983, a linkage on chromosome 4 was established and in 1993 the gene for HD was found. That period marked a tremendous increase in interesting HD and neurogenetic disorders. For the first time actual premanifest diagnoses could be made and as more diseases involving trinucleotide repeats of CAG were found, HD served as a model for many studies in medicine. CAG (cytosine (C), adenine (A), and guanine (G), is a trinucleotide, the building stone of DNA. CAG is the codon for the amino acid glutamic. (2)

**History of Huntington**

**Epidemiology** (3)

Huntington’s disease shows a stable prevalence in most populations of white people of about 5–7 affected individuals per 100000. Exceptions can be seen in areas where the population can be traced back to a few founders, such as Tasmania and the area around Lake Maracaibo21 in Venezuela. Currently, the higher incidence of Huntington’s disease in white populations compared with African or Asian people relates to the higher frequency of huntingtin alleles with 28–35 CAG repeats in white individuals.
### Table 1: History of Huntington Disease (3)

<table>
<thead>
<tr>
<th>Years</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1374</td>
<td>Epidemic dancing mania described</td>
</tr>
<tr>
<td>1500</td>
<td>Paracelsus suggests CNS origin for chorea</td>
</tr>
<tr>
<td>1686</td>
<td>Thomas Sydenham describes post-infectious chorea</td>
</tr>
<tr>
<td>1832</td>
<td>John Elliotson identifies inherited form of chorea</td>
</tr>
<tr>
<td>1872</td>
<td>George Huntington characterises Huntington’s disease</td>
</tr>
<tr>
<td>1953</td>
<td>DNA structure elucidated</td>
</tr>
<tr>
<td>1955</td>
<td>Huntington’s disease described in Lake Maracaibo region of Venezuela</td>
</tr>
<tr>
<td>1967</td>
<td>World Federation of Neurology meeting on Huntington’s disease</td>
</tr>
<tr>
<td>1976</td>
<td>First animal model (kainic acid) of Huntington’s disease described</td>
</tr>
<tr>
<td>1983</td>
<td>Gene marker for Huntington’s disease discovered</td>
</tr>
<tr>
<td>1993</td>
<td>HD gene identified, Huntington study group formed for clinical trials</td>
</tr>
</tbody>
</table>

**Figure 1: Transfer of Huntingtin gene.**

**Type of hunting tons disease (4)**

1. Juvenile Huntington’s disease; JHD.
2. Adult on set hunting tons disease.

**Typical Initial Signs & Symptoms of Juvenile HD (4) (5) (6)**

- Positive family history of HD, usually in the father.
- Stiffness of the legs.
- Clumsiness of arms and legs.
- Decline in cognitive function.
- Changes in behaviour.

**TYPICAL SIGNS & SYMPTOMS OF ADULT HD**

**Behavioural difficulties and symptoms in patients with Huntington’s disease (7)**

- Apathy or lack of initiative
dysphoria
irritability
Agitation or anxiety
Poor self-care
Poor judgment
Inflexibility
Weight loss,

**Frequent symptoms (20–50% of patients)**
- Disinhibition
- Depressed mood

**Cognitive/Intellectual changes (8)**
- Slight intellectual changes.
- reduced ability to organize routine matters
- Short-term memory loss long-term memory generally stays intact.
- Work tasks become more difficult.

**Emotional Changes (7)(8)**
- Recognizing is already lost.
- Hostility/irritability.
- Lack of energy
- Ongoing disinterest in life (lack of pleasure or joy)
- Bipolar disorder (manic-depression)

**Metabolic symptoms (8)**
- Catabolic weight loss.
- Endocrine dysfunction and sleep disturbance.

**Stages of HD (6)**

**Early stage**
Early in the disease, manifestations include subtle changes in coordination, perhaps some involuntary movements, difficulty thinking through problems, and often, a depressed or irritable mood. At this stage, medications are often effective in treating depression and other emotional symptoms. It is a good time to begin planning for the future. Financial plans should be made and legal documents (a Living Will, for example) drawn up.
Middle stage
Involuntary movements (chorea) may become more pronounced. A staggering gait can sometimes be mistaken for drunkenness. Speech and swallowing will begin to be affected. Likewise, occupational and physical therapists can develop programs to help maintain the highest level of functioning and thereby improve the quality of life. Thinking and reasoning skills will also gradually diminish. At this stage it may become increasingly difficult.

Late-stage
HD may have severe chorea, but more often have become rigid. Choking on food becomes a major concern, as does weight loss. At this stage people with HD are totally dependent on others for all aspects of care, can no longer walk, and are not able to speak. Although cognitive abilities are severely impaired, it is important to remember that the person is generally still aware of his/her environment, remains able to comprehend language, and retains an awareness of loved ones and others. People do not die from HD itself but rather from a complication of the disease, such as choking or infection. Death generally occurs about 15 to 20 years after onset.

DEVELOPMENTAL STAGES OF HD (9)

Table 2: Stages during the life of a Huntington’s disease patient

<table>
<thead>
<tr>
<th>Stages during the life of a Huntington’s disease patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Preclinical stage</strong></td>
</tr>
<tr>
<td>A1. At-risk stage (50%), one affected parent - Anxiousness for the future</td>
</tr>
<tr>
<td>- Uncertainty about carriership</td>
</tr>
<tr>
<td>- Care for affected parent</td>
</tr>
<tr>
<td>A2. Gene carrier, premanifest stage - Certainty about carriership</td>
</tr>
<tr>
<td>- New position in the family</td>
</tr>
<tr>
<td>- Renewed uncertainty about onset</td>
</tr>
<tr>
<td>- Care for affected parent and own family</td>
</tr>
<tr>
<td>A3. Transition phase - Strong feelings about changes in cognition</td>
</tr>
<tr>
<td>- Changes in behaviour</td>
</tr>
<tr>
<td>- Changes in motor activity</td>
</tr>
<tr>
<td>- Uncertainty remains</td>
</tr>
<tr>
<td><strong>B. Clinical stage</strong></td>
</tr>
<tr>
<td>B1. Clinical stage I - Presentation first symptoms: neurological, cognitive or psychiatric</td>
</tr>
<tr>
<td>- Chorea most prominent symptom</td>
</tr>
<tr>
<td>- Independent in ADL</td>
</tr>
<tr>
<td>- Burden for the family mainly psychological</td>
</tr>
<tr>
<td>- Rare death, unless suicide</td>
</tr>
<tr>
<td>B2 Clinical stage II - Motor disturbance more generalised</td>
</tr>
<tr>
<td>- Physical dependence starts</td>
</tr>
<tr>
<td>- Burden for family psychological and physical</td>
</tr>
</tbody>
</table>
NEUROPATHOLOGY (3)

- Death by other cause, suicide, euthanasia

B3. Clinical stage III - Severe generalised motor disturbance
- Almost complete physical dependence
- Patient completely dependent on care

- Death by other cause, suicide, euthanasia

- Death by other cause, suicide, euthanasia

NEUROPATHOLOGY (3)

- Neuropathological changes in Huntington’s disease are strikingly selective, with prominent cell loss and atrophy in the caudate and putamen. Striatal medium spinyneurons are the most vulnerable.

- Those that contain enkephalin and that project to the external globus pallidum are more involved than neurons that contain substance P and project to the internal globus pallidum. Interneurons are generally spared.

- These findings accord with the hypothesis that chorea dominates early in the course of Huntington’s disease because of preferential involvement of the indirect pathway of basal ganglia-thalamocortical circuitry.

- Other brain areas greatly affected in people with Huntington’s disease include the substantia nigra, cortical layers 3, 5, and 6, the CA1 region of the hippocampus, the angular gyros in the parietal lobe, Purkinje cells of the cerebellum, lateral tuberal nuclei of the hypothalamus, and the centro medial parafascicular complex of the thalamus.

- In early symptomatic stages of Huntington’s disease, the brain could be free of neurodegeneration. However, evidence of neuronal dysfunction is abundant, even in asymptomatic individuals. Cortical neurons show decreased staining of nerve fibres, neurofilaments, tubulin, and microtubule-associated protein 2 and diminished complex in 2 concentrations.

- These elements are associated with synaptic function, cytoskeletal integrity, and axonal transport and suggest an important role for cortical dysfunction in the pathogenesis of the disorder.

- One of the pathological characteristics of Huntington’s disease is the appearance of nuclear and cytoplasmic inclusions that contain mutant huntingtin and polyglutamine.

- Although indicative of pathological poly glutamine processing, and apparent in affected individuals long before symptom onset, 43 mounting evidence suggests that these inclusions are not predictors of cellular dysfunction or disease activity, which instead seem to be mediated by intermediate stages of poly glutamine aggregates.
NEUROPATHOLOGICAL FEATURES (2)

Non–Central Nervous System Changes

- As with the other polyglutamine disorders, HD is primarily a disorder of the central nervous system (CNS). Huntingtin is expressed in many tissues, but the clinical features of HD reflect CNS dysfunction, and almost all histopathologic abnormalities are restricted to the brain.

- It is important to note that although clinical features and traditional histopathologic analyses point to HD as a CNS disease, investigations with more sensitive measures point to widespread, albeit, effects of expanded htt. Studies of peripheral blood and lymphoblasts derived from HD subjects have revealed aberrant gene regulation and mitochondrial abnormalities.

- A recent study of urea cycle metabolites suggests a subclinical but detectable effect of expanded on hepatic function. Several studies suggest abnormalities of another long-lived postmitotic tissue, muscle.

- Gene regulation studies, magnetic resonance spectroscopic studies, and biochemical studies suggest muscle mitochondrial abnormalities in HD, and muscle biopsy histology indicates the presence of significant but nonspecific abnormalities.

- An interesting recent observation is the description of testis abnormalities in HD. Testes are characterized by high-level expression of HTT mRNA. Describe reduced numbers of germ cells and abnormal seminiferous tubule morphology.

![Figure 2: A model of HD pathogenesis.](image-url)
The importance of CAG repeats
One of the important early triumphs of modern molecular biology has been the demonstration that the underlying cause of HD is the expansion of a CAG repeat sequence in the first axon of a gene on chromosome 4, which encodes the protein huntingtin. CAG is the codon for glutamine (Q in the single letter code for amino acids). The normal range for the number of Qs in the polyglutamine tract (polyQ) is between six and 34, with disease being found when polyQ is greater than 40.

![Diagram of CAG repeats and huntingtin protein aggregates](image)

Figure 3: The proposed mechanism for the expression of huntingtin protein aggregates and their possible effect on nerve cells (1)

CLINICAL GENITICS
The gene for Huntington’s disease (HD) is located on the short arm of chromosome four and is associated with an expanded trinucleotide repeat. Normal alleles at this site contain CAG repeats, but when these repeats reach 41 or more the disease is fully penetrant. Incomplete penetrance happens with 36–40 repeats, and 35 or less are not associated with the disorder. The number of CAG repeats accounts for about 60% of the variation in age of onset, with the remainder represented by modifying genes and environment. Trinucleotide CAG repeats that exceed 28 show instability on replication, which grows with increasing size of the repeat; most instability leads to expansion (73%), but contraction can also take place (23%). Instability is also greater in spermatogenesis than oogenesis, in that large expansions of CAG repeats on replication happen almost exclusively in males. These findings account for the
occurrence of anticipation, in which the age of onset of Huntington’s disease becomes earlier in successive generations, and the likelihood of paternal inheritance in children with juvenile onset symptoms. Similarly, new-onset cases of Huntington’s disease with a negative family history typically arise because of expansion of an allele in the borderline or normal range (28–35 CAG repeats), most usually on the paternal side. Somatic instability of CAG repeats also happens in Huntington’s disease. Although fairly minor, somatic mosaicism with expansion has been noted in the striatum in human beings and in animal models of the disease, and this finding could contribute to selective vulnerability. (3)

THE ROLE OF HUNTINGTIN IN HD
Huntingtin has no great structural homology with other human proteins, so determination of its normal function has proved difficult. Changes seen in embryonic stem cells of huntingtinknockout mice indicate that it is essential for normal nuclear and perinuclearorganelles and that one factor regulating its synthesis is iron. The protein (~349 kDa) is composed of approximately 3150 amino acids (depending on the size of the polyQ tract). As with many other large proteins, huntingtin is made up of repeated structures. The polyQ tract starts at residue. The protein is widely distributed throughout the central nervous system (CNS), and this has opposed the question of how its altered functioning gives rise to selective neuronal loss in HD.

Initially, the most likely explanation was thought to be that the huntingtin gene mutations confer a “deleterious gain of function”, with the concept of loss of function gaining ground more recently, although how the variant huntingtinss go on to cause neurodegeneration has remained a mystery. (10)

A NOVEL PROPERTY OF MUTANT HUNTINGTIN
Mounting evidence indicates that the novel property of mutant huntingtin involves a special conformation of the N-terminal region. The elongated glutamine tract has adisproportionate impact on reducing the migration of huntingtin in gel electrophoresis and reacts preferentially with certain monoclonal antibodies that fail to detect normal huntingtin. In a small N-terminal fragment, the elongated polyglutamine promotes self-aggregation in an test-tube reaction in a manner that converts the glutaminetract to a b-sheet conformation diagnostic of insoluble amyloid. The threshold, progressivity and dominance characteristics of this reaction match the criteria outlined above for involvement in triggering disease pathogenesis, suggesting that it measures the crucial property of themutant protein. However,
it does not reveal whether this property acts within cells via aggregation of a small fragment or acts within the full-length protein via some other effect, perhaps on protein–protein interactions that establish neuronal specificity. Many of the proteins shown to interact with the N-terminus of huntingtin show differential binding to the normal and mutant versions, raising the possibility that a striatal-specific interaction of this type might mediate pathogenesis. (11)

**DIAGNOSIS**

**Diagnosis Using Various Methods (5, 3)**

- The current gold standard is DNA determination, showing a CAG-repeat of at least 36 on the huntingtin gene on chromosome 4.
- Biomarkers (clinical, blood, MRI) and hence the transition determining parameters.

**TESTING**

DNA analysis can be used to confirm the diagnosis. Tests are available to identify whether someone has the faulty gene. Genetic testing can diagnose Huntington’s disease at every stage of the life cycle it is of three types: antenatal or prenatal, pre-symptomatic and confirmatory testing. (7)

**Antenatal or Prenatal Testing**

Either amniocentesis (a sample of fluid from around the fetus), or chorionic villus sampling (CVS)—a sample of fetal cells from the placenta will indicate whether the body has inherited the gene for Huntington’s disease. Antenatal tests are carried out early in pregnancy on the unborn children of couples from families affected by Huntington’s disease. They can be used to calculate the risk of that child going on to develop the disease in their adult life. Again, the implications of positive results are serious and couples need advice and support from a specialist doctor or counselor to help them in their decisions.

**Pre-symptomatic Testing**

These are available to the people who are at risk of inheriting Huntington’s from a parent, but do not have symptoms and don’t know whether or not they carry the gene. Pre-symptomatic tests are carried out in people who are not showing symptoms of Huntington’s disease, but have a family history of it.
Confirmatory Testing
This determines whether a person showing what appear to be the symptoms of Huntington’s disease, actually has the disease. Neurological and psychological tests are also conducted to arrive at a conclusive diagnosis of Huntington’s disease.

Potential risks of premature gene testing in a child
Incorrect attribution of symptoms to HD, Failure to make the correct diagnosis, Stigmatizing the child, Insurability, Psychological effects on the child. (9)

Figure 4: Statistical parametric map showing grey matter volume loss in patient groups compared with controls. Pre-A and pre-B are premanifest Huntington’s disease gene carriers with estimated time to clinical disease onset greater than and less than 10.8 years, respectively. (12)

THERAPIES EMPLOYED FOR HD
The most commonly used therapies in HD patients are symptomatic drug therapies and no therapy has been developed that effectively modifies disease progression. (13)

Physical Therapy in juvenile HD
- Home/school exercise program
- Gait evaluation
- Management of rigidity and spasticity
Occupational therapy in juvenile HD

- Safety evaluation
- Assessment of activities of daily living
- Assistive devices
- Modification of food textures

Speech therapy

- Outpatient or home speech therapy/oral exercise
- Training with assistive devices
- Assessment of dysphasia
- Strategies to avoid choking

Physical Therapy

- Daily exercises to maintain range of motion.
- Heat, massage and stretching
- Loosen muscles with spasticity or rigidity.

DRUG BASED MANAGEMENT OF HD

Dopamine Depletion (14)

Abnormal movements in HD occur as a result of increased activity via the direct circuit and decreased activity via the indirect circuit, both mediated by dopamine. Logically blocking the effects of dopamine should reduce choreic movements. Traditionally, typical neuroleptics were used to treat chorea but severe side effects associated with treatment led many to discourage their widespread use. The atypical neuroleptic, clozapine binds to dopamine receptors and blocks dopamine binding and subsequent signaling. When tested in a double-blind placebo-controlled clinical trial clozapine was only effective in reducing dyskinesias in patients that had no prior exposure to neuroleptics. Higher doses were required for reasonable effectiveness and these high doses were poorly tolerated in most patients. Evidence from small open label series supports the use of other atypical antipsychotics in HD. These include olanzapine. Tetrabenazine acts by preventing the packaging of dopamine into vesicles, thereby suppressing its presymptomatic release. It also prevents dopamine signaling by blocking postsynaptic dopamine receptors.
- **NMDA Receptor Antagonists**

The moderate effectiveness of antidopaminergic therapies may be outweighed by debilitating side effects like parkinsonism, tardive dyskinesias, and severe depression. An alternative strategy is to use NMDA receptor antagonists. It has been thought for some time that levodopa-induced dyskinesias in Parkinson’s disease (PD) occur as a result of increased NMDA receptor sensitivity and are reduced by treatment with NMDA receptor antagonists. The fact that dyskinesias in PD are clinically similar to chorea seen in HD provided the theoretical framework that NMDA antagonists may be effective in reducing chorea in HD. A second NMDA antagonist, memantine, has also been tested in clinical trials for HD. Memantine may be preferred to amantadine because it has a longer half-life, allowing for once daily dosing. While memantine was effective in treating chorea, it did not have any effects on cognition or behaviour. (14)

**Rigidity**

Medications which may help to reduce rigidity include anticholinergic drugs, such as trihexyphenidyl, and carbidopa-levodopa. Levodopa is likely to worsen chorea in those who have it and must be used very carefully for that reason.

**Spasticity/Dystonia**

Antispasticity drugs include lioresal, tizanidine, diazepam, and dantrolene, all of which must be used carefully because of the potential side effects. Local injection of botulinum toxin into the affected muscle might be attempted.

**Table 3: Non-Drug Based Management of Huntington’s Disease (8)**

<table>
<thead>
<tr>
<th>Feature of disease</th>
<th>Examples of management measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait disturbance and chorea</td>
<td>Physiotherapy to optimise and strengthen gait and balance, and to assess for walking aids; occupational therapy assessment to modify home environment and improve safety; weighted wrist bands to combat limb chorea</td>
</tr>
<tr>
<td>Cognitive symptoms</td>
<td>Ensure every day has a structure to overcome apathy and difficulty in initiating activities (occupational therapy can advise on this); maintain routines to reduce need for flexibility</td>
</tr>
<tr>
<td>Social problems</td>
<td>Carers to help at home, residential or nursing home care, day centres to maintain social interactions</td>
</tr>
<tr>
<td>Communication</td>
<td>Speech and language therapy to optimise speech and later in disease to assess for communication aids; ensure patient has time to comprehend and respond to speech, and that information is presented simply</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Speech and language therapy to advise on safest food</td>
</tr>
<tr>
<td>Psychological problems</td>
<td>Develop strategies to deal with cognitive and emotional challenges of disease using counselling or cognitive behavioural therapy</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>

**Chorea**

Haloperidol, risperidone, olanzapine, or pimozide can be used, though these agents tend to make rigidity worse.

**Essential fatty acids**

Essential fatty acids are present in phospholipids of cellular membranes and are diminished in patients suffering from tardive dyskinesias. Consequently, members of the essential fatty acids family, like linoleic acid and dihomogammalinolenic acid, have been used to treat dyskinesias. In a randomized, double-blind, placebo-controlled trial of HD, a combination of highly unsaturated fatty acids (HUFA) was used to treat motor and cognitive symptoms in postsymptomatic patients. Patients showed a significant improvement in dyskinesias and in the motor component of the Unified Huntington’s Disease Rating Scale (UHDRS). (11)

**Cystamine & cysteamine**

These drugs decrease the activity of a group of enzymes called transglutaminases. These enzymes are thought to be involved in the formation of huntingtin aggregates the lumps of protein that are seen in unhealthy brain cells in HD (12).

**Autophagy enhancers**

Autophagy is a clearance process that cells use to get rid of unwanted proteins. HD researchers think that the abnormal protein in HD, huntingtin, is disposed of using autophagy. Looking for drugs that make autophagy happen more efficiently might help cells get rid of huntingtin and live longer. Rapamycin belongs to a group of drugs called mTOR inhibitors, which activate autophagy, and it has been shown to slow down HD in a mouse model. (5)

**Inflammation and the KMO pathway**

Microglia is the brain’s immune system cells, like white blood cells that protect the body against infections. Our own research has shown that the immune system is overactive in HD,
and evidence is mounting that microglia are overactive, too. (5)

**Caspase inhibitors**

In cells, the abnormal HD protein (huntingtin) is cut into smaller proteins by enzymes called caspases. Some of the smaller fragments that are produced by this are more damaging to cells than the original full-length huntingtin. (5)

**P53 pathway**

P53 is a cell protein with many functions, but it’s known to be involved in energy production, the response to stress and controlling when cells divide. Recently, it has been shown that p53 accumulates in the brain cells most affected by HD, and that the huntingtin protein and p53 interact with each other. (5)

**Neuroprotective therapies**

Neuroprotective strategies are designed to modify disease progression based on the concept of neuronal preservation. It is likely that disease-modifying strategies will ultimately be a more powerful approach relative to symptomatic treatments. These therapies attempt to attenuate or delay the onset of symptoms by preventing cell death and preserving neuronal circuitry in vulnerable brain regions. Neuroprotective therapies can be delivered in a systemic fashion. (14)

**Coenzyme Q10**

Coenzyme Q10 is a molecule in the electron transport chain that carries electrons from complex I and II to complex III. By keeping electrons with the enzymes in the mitochondrial membrane, coenzyme Q10 reduces formation of reactive oxidative species and oxidative stress.

Mitochondrial energy impairments plague brain cells in HD, resulting in neuronal death and dysfunction. Targeting enzymes or cofactors that play a role in energy production theoretically could help reduce cell death. (14)

**Creatine**

Creatine has been hypothesized to be effective as a therapy for HD because it is capable of buffering ATP levels in cells. Mitochondrial enzymes, and therefore ATP production, are disrupted in HD brains. When creatine is ingested it is converted into phosphocreatine and stored. *Brain-Derived Neurotrophic Factor (BDNF)* (14) is a neurotrophic factor that is
produced by cortical neurons and is essential for survival of striatal neurons. BDNF is transported in vesicles along microtubules with the help of wild-type huntingtin protein. Either a reduction in wild-type huntingtin or the expression of mutant huntingtin disrupts transport of BDNF, resulting in a loss of trophic support to striatal neurons. Additionally, in striate neurons, wild type huntingtin protein enhances the expression of BDNF and expression of mutant huntingtin reduces BDNF levels and this effect is toxic to neurons. (14)

**RNA Interference (RNAi)**

A recently developed therapy that has come to the forefront in HD is RNAi. This therapy attempts to use short interfering RNA (siRNA), short hairpin RNA (shRNA), or microRNA (miRNA) molecules to shutdown the production of the mutant huntingtin protein. (14)

**NEURORESTORATION & TRANSPLANTATION THERAPIES**

Although HD is a genetic disorder that can be detected prior to the onset of symptoms, most patients do not consult a physician until after they develop signs of the disease. At this stage, there likely is extensive cell death in the striatum. In such cases a neuroprotection therapy may not be ideal. In contrast, a therapy in which lost cells are replaced might be more efficient for these patients who are in later stages of the disease. It has been shown over 20 years since the first demonstration of successful brain transplantation in animal models of HD.

Perhaps one of the most critical experiments was one of the first, where Isacson and coworkers grafted fatal ganglion eminence into the striatum of rats that had previously received bilateral excitotoxic lesions of the striatum.

Not only did the grafts survive and improve motor function, they also improved cognitive function. This is one of the first demonstrations that restoring function in a manner limited to the striatum can improve higher order cognitive function. (14)

**Human Fetal Tissue Transplants**

Several clinical studies have been completed that used human fatal tissue transplants in HD patients. Selection of appropriate fatal tissue is essential for optimal therapeutic benefit, and isolation of tissue destined to a striatal fate is ideal for transplantation therapies. The Network of European CNS Transplantation and Restoration examined human foetuses to determine the location of striate neurons and the time course of differentiation. This group determined that DARPP-32-positive striatal neurons begin to develop at week 7 postconception in the
ganglion eminence. At 8.5 weeks post conception the lateral ganglion eminence separates from the medial ganglionic eminence.

Alternative Transplantation Studies
Due to the limited availability of embryonic or fatal stem cells for therapy many researchers are looking into alternative donor sources for transplantation. Such sources of stem cells are derived from umbilical cord blood, bone marrow, and adult sources like the sub ventricular zone and dentate gyros. (14)

CELL DEATH
- In HD, cell death occurs primarily in medium-sized spiny neurons in the striatum, a population that expressesaminobutyric acid (GABA) as their neurotransmitter. These cells comprise approximately 95% of the neurons in the striatum and specific subpopulations of medium spiny neurons coexpress either substance P or enkephalin. There is a selective vulnerability for these two populations of neurons in early and late disease states.
- In the early stages of the disease process, neurons that coexpress enkephalin and project to the globus pallidus via the indirect pathway are particularly vulnerable. In normal circuitry the indirect pathway is involved in the inhibition of voluntary movements. Death of the enkephalin neurons causes an activation of the premotor and supplementary motor cortices and produces the hallmark hyperkinetic, choreiform movements seen in HD.
- In later stages of the disease, death occurs in the neurons that coexpress substance P and project to the globus pallidus via the direct circuit. This pathway is normally involved in the initiation of voluntary movements. Death of substance P neurons blocks the activation of the premotor and supplementary motor cortices, producing hypokinetic symptoms. Other populations of interneurones like the large cholinergic and medium a spiny neurons are spared in the diseased brain. (15)

FUTURE PERSPECTIVES
Huntington’s disease is a physically, psychologically and socially devastating disorder. Knowledge about the disease and care for patients has increased enormously over the last two decades. As the mean duration of illness is more than 17 years, one tends to forget the many years prior to the onset of symptoms during the at-risk and the preclinical periods, or the premanifest period. Huntington’s disease is a lifelong disease for both the individual and the family. From the moment the gene was localised in 1983, and particularly after 1993,
attention has focussed on the pathophysiological pathway with the aim of developing a
therapy. Currently, in several observational studies of at-risk individuals, the feasibility of
using the onset of the clinical Huntington’s disease phenotype or other biomarkers of disease
(such as changes on imaging studies) is being investigated as a potential endpoint for future
clinical trials.

CONCLUSION
There are several exciting therapies for HD currently under testing. However, no one
therapy has been show to combat all of the symptoms associated with the disease: cognitive,
motor, and psychiatric. Additionally, a treatment would have to be either neurorestorative or
neuroprotective and increase survival. Hence the symptoms can be minimised & thus quality
of life could be improved to combat HD.

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