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HUNTINGTON'S DISEASE: A RARE NEURODEGERATIVE DISORDER

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ABSTRACT

Huntington's disease (HD) is a rare neurodegenerative disorder of the central nervous system, with a genetic autosomal-dominant inheritance, that first involves basal ganglia (caudate nucleus and putamen) and results from expansion of a CAG trinucleotide repeat in the HTT (huntingtin) gene: alleles with 40 or more repeats are fully penetrant. The disease is characterized by motor, cognitive and psychiatric disorders, and a range of somatic symptoms. The classic sign is Chorea that gradually spreads to all muscles. Mean age onset of symptoms is 30-50 years. In some cases symptoms start before the age of 20 years with behavior disturbances and learning difficulties at school (Juvenile Huntington's Disease). Progressive worsening leads to a bedridden state with cognitive deterioration. The prevalence of the clinical syndrome is 37:100,000 whereas nearly 20:10,000are carriers of the gene responsible for the disease. Death occurs about 20 years after the onset of symptoms. More than a century after the first description of Huntington's disease (HD), there is still no curative treatment of the disease; however, symptomatic treatments are thought to be efficacious in controlling some of its troublesome symptoms. Yet, symptomatic management of HD remains inadequately documented, which may lead to variations in care mainly based on clinical experience and not on scientific evidence. HD is presently the most widely studied genetic neurodegenerative disease that has diagnostic and predictive genetic testing, with the possibility of gene-targeted therapy in the near future.

Scientifically supported and consensual pharmacological, surgical and non-pharmacological recommendations for the treatment of HD have been provided.

KEYWORDS: Huntington's disease (HD), Neurodegenerative disorder, Genetic autosomal-dominant inheritance, Basal ganglia (caudate nucleus and putamen), CAG trinucleotide, HTT (huntingtin), Motor, cognitive and psychiatric disorders, Chorea, Juvenile Huntington's Disease, Gene-targeted therapy, Pharmacological, Surgical, Non-pharmacological.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant, late onset neurodegenerative disorder characterized by motor abnormalities, cognitive dysfunction, and psychiatric symptoms.[1] While it has been known by various names previously, it obtained its eponym after George Huntington presented an exhaustive description of the clinical manifestation of the disease in 1872.[2]

Although it was called Huntington's chorea for nearly a century, it is now more accurately referred to as Huntington disease, because chorea is neither a constant nor a particularly dominant feature of the disease. It is a neurodegenerative disorder passing within families from generation to generation with onset in middle age and characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia.[3] In 1983, a linkage on chromosome 4 was established and in 1993 the gene for HD was found.[4]

In the brain, the basal ganglia is highly affected which organize muscle driven movements of the body or motor movement. The disease is characterized by a primary progressive loss of medium spiny projection neurons within the basal ganglia.[5] symptoms and signs of Huntington's disease consists of motor, cognitive and psychiatric disturbance.

The prevalent debilitating features of HD include weight loss, sleep and circadian rhythm disturbance and autonomic nervous system dysfunction. The mean age of onset is between 30 and 50 years. The mean duration of the disease is 17-20 years.

The progression of the disease leads to more dependency in daily life and finally death. Genetically, Huntington's disease is caused by expanded CAG repeat in the Huntington gene which encodes abnormally long polyglutamine delayed onset, selective neuronal vulnerability, abnormal protein aggregation and processing and cellular toxic effects involving both cell autonomous and cell interaction.[6]

Management should be multidisciplinary and it is based on treating symptoms with a view to improving quality of life. Chaorea is treated with dopamine receptor blocking or depleting agents. Medication and non-medical care for depression and aggressive behavior may be required.

The progression of the disease leads to the complete dependency in daily life, which results in patients requiring full-time care, and finally death. The onset ages from Huntington disease have nonlinear inverse relationship with the number of polyglutamine repeat sequences in the gene mutation so that younger d diagnosed patients tend to have longer repeat length.[7]

Despite the fact that the pathogenesis of Huntington's disease has still not been resolved and is not available, many therapeutic options are available for treating symptoms. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms.

Drug treatment is therefore individualized and based on expert opinion and daily practice. Although any signs and symptoms can be treated, it is not always necessary to do so. The patient limitation in daily life determines whether the drugs are required or not.[8]

Hd Phenotypes

The defining phenotype of HD is generally considered to be chorea, involuntary movements, some dance-like, that occur in many parts of the body. Individuals with the disease frequently also display psychiatric symptoms, most commonly depression and irritability, as well as declines in cognitive abilities. It seems likely that people with HD have a variety of still-being-characterized behavioral changes; for example, recently, the occurrence of abnormal sleep patterns was documented in the laboratory, although patients and families usually complain of this symptom as well.[9]

Huntington Disease

Huntington disease has 3 subtypes, with the adult-onset being the most common and the juvenile and infantile varieties being far less prevalent. In adult-onset HD, the disease is characterized by a triad of behavioral, cognitive, and motor features.[10] Behavioral symptoms often present early as increased irritability, agitation, loss of inhibition, and increased aggression. In a patient without a definite family history, definitive diagnosis with these symptoms is often delayed. However, diagnosis is often easier with evidence of motor symptoms.

These include chorea, which can become less pronounced with the onset of rigidity and dyskinesia; motor impersistence (the inability to maintain a sustained voluntary muscle contraction); and loss of fine and gross motor skills, which respectively occur in the early and late phase of the disease.[11] Rigidity and dyskinesia along with cognitive decline are dominant features with chorea rarely seen.[12]

Patients are no longer able to express themselves. Revealing the patients unmet needs is therefore hindered and this might lead to irritability, impulsive and unwanted behavior cause much distress for patients and caregivers. Because of behavioral symptoms, cognitive decline and the inability to express oneself, psychosocial problems develop.

Psychosocial stressors may include feelings of sadness and anxiety about the cognitive and physical decline and about changes in social roles. The gradual deterioration in communication skills in combination with the behavioral problem inpatient with HD contribute to a decrease of functional help and a progressive inability to participate in various life situations leading to loss of quality of life.[13]

This disorder is caused by CAG (Cytosine, Adenine, Guanine) trinucleotide repeats in the 50 coding region of the IT15 (Interesting Transcript15) gene located on locus 4p16.3.[14] HD expanded alleles have more than 36 CAG units in the HD gene, whereas normal individuals have from 10–35 CAG units.[15]

This mutation generates a functionally defective protein called huntingtin (HTT), a protein of uncertain molecular function(s).[16, 17] HTT is a ubiquitously expressed protein that is located throughout the body. Mutant HTT, which contains pathologically extended polyglutamines, causes the earliest and most dramatic neuropathological changes in the neostriatum and cerebral cortex[16], whereas a loss of wild-type HTT function contributes to disease development.[18-22]

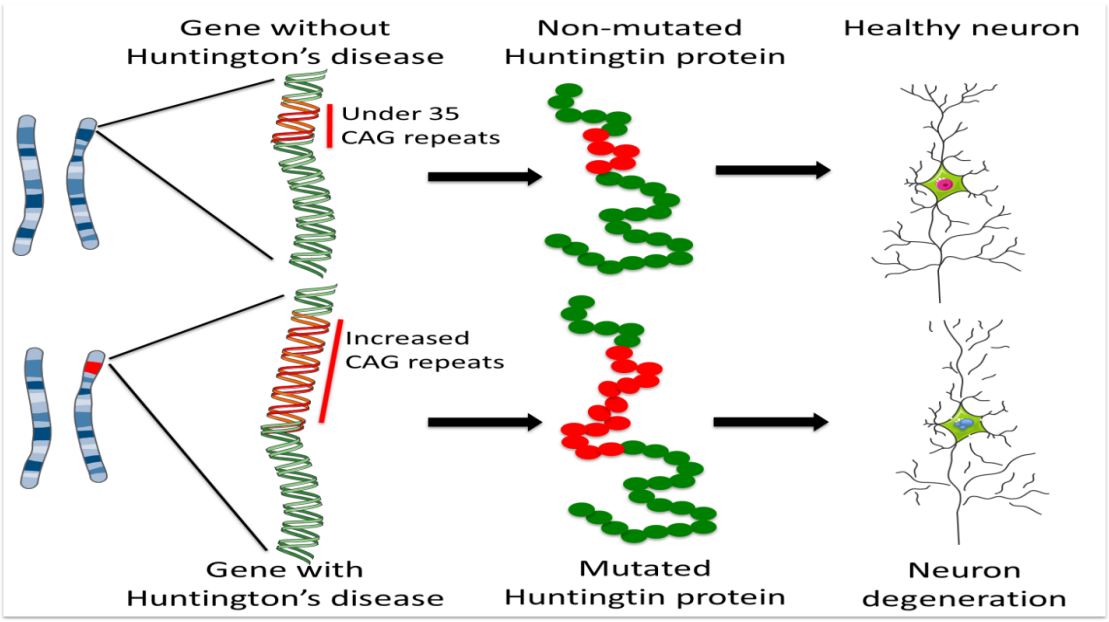

Figure 1: Genetics of Huntingtin protein.

HOW IS HUNTINGTON PASSED ON?

When a parent has the faulty Huntington's gene, each child has a 50% chance of having that gene passed onto them. If both parents have a faulty Huntington's gene this means that each of their children will have a higher risk of getting Huntington's. In some rare cases if one parent has two faulty Huntington's genes then all of their children will develop Huntington's. If both parents have a faulty Huntington's gene, this means that each of their children will have a higher risk of getting Huntington's.

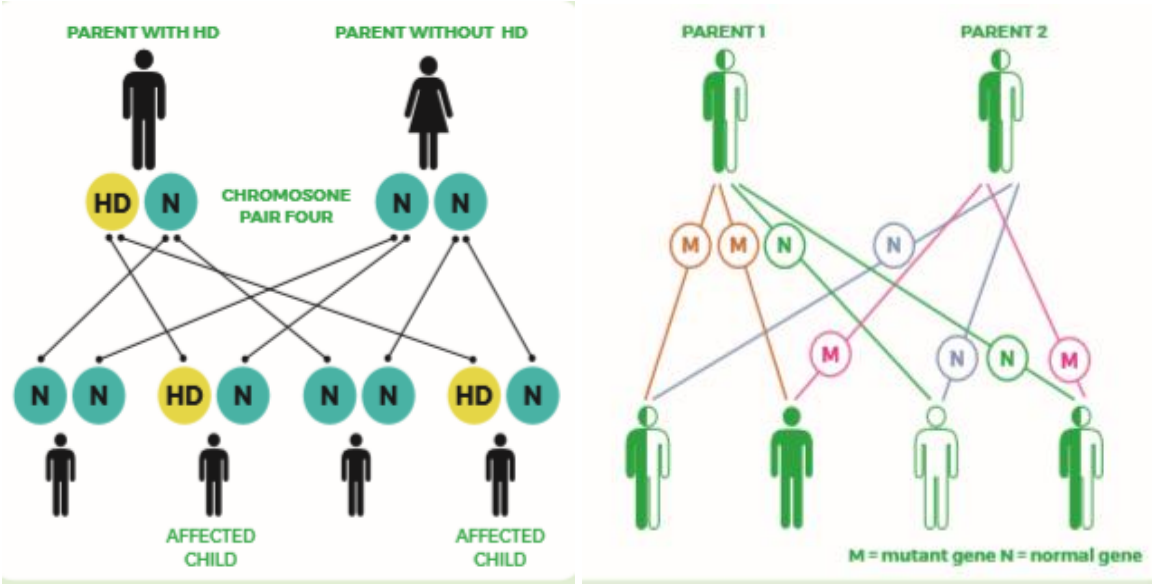

Figure 1: Inheritance of Huntington Disease.

Biochemical Properties and Functions of Huntingtin

Huntingtin is highly conserved from Drosophila to mammals including humans, suggesting that it has a central role in cell functioning. Its broad subcellular distribution implies that it functions at several intracellular sites. Wild-type huntingtin is located mainly in the cytoplasm[23], is partly affiliated with membranous profiles[24] and binds to b-tubulin and microtubules[25,26] Among the membrane compartments with which huntingtin is associated, synaptic vesicles[23,24], recycling endosomes, endoplasmic reticulum, Golgi complex and clathrin-coated vesicles[27] have an abundance of the protein. Taken together, the evidence suggests that wild-type huntingtin has a role in membrane trafficking in the cytoplasm and is also involved in microtubule-based axonal transport. In addition, huntingtin is found in the nucleus and seems to be vital for ontogenic development.[28]

Table 1: Huntington- interacting proteins.

Name	Binding region in huntingtin	Functions	Effects caused by huntingtin mutation	Refs
Transcriptional co-repressor C-terminal binding protein	At PXDLS motif	Transcriptional regulation	Repressed transcription	33
N-CoR	N terminus of htt171	Transcriptional regulation	CAG repeat length dependent binding	34
CBP and p^{53}	N terminus	Transcriptional regulation	Depleted from nucleus and present in aggregates; decreased transcription	35, 36, 37
Sp^{1}	N terminus	Transcriptional regulation	Enhanced interaction; disrupted interaction between Sp1 and TAFII130	38,39
Gln-Ala repeat transcriptional activator (CA150)	Full-length huntingtin	Transcriptional regulation	Marked increase of CA150 expression	40
CIP4	N terminus	Involved in Cdc42 and WASp-dependent signal transduction	Marked CIP4 overexpression and cell death induction of striatal neurons	41
NF-kB/Rel/dorsal family transcription factor	C terminus	Nuclear transport	?	42
HAP1	N terminus	Endosome–lysosome trafficking	Enhanced binding	43
HIP1	N terminus	Clathrin-mediated endocytosis via binding to clathrin and AP2; promotes	Ruuced interaction	44-46

		clathrin assembly; does not bind to actin		
HIP1-related/HIP12	Does not interact with huntingtin but can interact with HIP1	Acts as functional link between clathrin and actin; promotes actin organization and clathrin assembly		46-47
HIP14	N terminus	Intracellular trafficking and endocytosis	Decreased interaction	48
Hippi	Binds to HIP1	Mediates apoptotic pathways.	Free HIP1 modulated by polyglutamine length in huntingtin; forms Hippi–HIP1 heterodimers and launches apoptosis	49
PACSIN I/syndapin	N terminus, proline-rich region	Binds to dynamin, synaptojanin and N-WASp	Enhanced interaction	50-52
Endophilins	Exon 1 protein, proline-rich region	Bind to lipids; acts as a lysophosphatidic acid acyl transferase; interacts with dynamin and amphiphysins	Enhanced binding to endophilin A3	53-54
PSD-95	N-terminal proline region	Binds and regulates the activity of glutamate receptors	Decreased interaction	55

Abbreviations: CA150, co-activator 150; CAG, Cys-Ala-Gly; CBP, CREB-binding protein; CIP4, cdc42-interacting protein 4; CREB, cAMP-response-element-binding protein; HAP1, Huntingtin-associated protein 1; HIP1, Huntingtin-interacting protein 1; HIP14, Huntingtin-interacting protein 14; Hippi, HIP1 protein interactor; htt, huntingtin; HYPA, htt yeast partner A; HYPB, htt yeast partner B; HYPC, htt yeast partner C; N-CoR, nuclear receptor co-repressor; PXDLS, Pro-Xaa-Asp-Leu-Ser; Sp1, specificity protein 1; TAF, TATA-binding protein-associated factor; WW, Trp-Trp.

Huntingtin-binding proteins

Wild-type huntingtin is a very large protein of 350 kDa that might be involved in several functions through its numerous binding partners (Table 1). Among these partners are proteins with important roles in transcriptional regulation, intracellular trafficking and cytoskeletal organization.

Many of the known huntingtin-binding proteins have roles in endocytosis, whereas comparatively few are involved in exocytosis. It is reasonable to propose that mutant huntingtin shows aberrant binding to individual interacting partners and, consequently, the

function of the specific interacting protein is disrupted. In addition to affecting the normal interactions between huntingtin and its regular binding partners, the mutation can also lead to novel protein interactions.

When huntingtin contains 37 or more consecutive glutamines, it misfolds and tends to form amyloid-like intracellular aggregates.[29]These aggregates can recruit several proteins, including those normally involved in synaptic function such as α-synuclein.[30] This might lead to a local depletion of components that are vital to the normal function of synapses.

Furthermore, the presence of huntingtin aggregates might lead to saturation or structural inhibition of the ubiquitin–proteasome system – the chief cellular proteolytic pathway that normally processes misfolded proteins.[31]

Functional inhibition of the ubiquitin–proteasome pathway might lead conceivably to an abnormal accumulation of both components of endocytic and/or autophagic pathway and synaptic proteins that would be digested by this proteolytic pathway as part of the normal turnover of cellular protein.[31,32]

PRECLINICAL STAGES OF HD

Recent studies have proved that the stages of HD include the time before a clinical diagnosis of the motor disorder. These precursor phases are: HD at risk , HD Expansion carrier, and HD Prodrome. There are various methods existing for measuring and assessing the progression of HD symptoms. One of the most commonly used is the Total Functional Capacity Rating Scale (UHRDS). This scale rates the persons level of independence in five domains: occupation, managing, finances, performing domestic chores, performing activities of daily living and setting for level of care. This score is used with the Shoulson and Fahn rating scale to determine the stage of diagnosed HD using I-IV scale, with a lower number indicating a higher level of function.

Precursors to HD: HD at risk –individuals whose parents with a diagnosis of HD who have not been tested are considered at 50% risk for HD. For persons to be considered at risk no signs or symptoms of HD are present.

HD Expansion Carrier: Persons who have gone a predictive genetic test for the HD causing CAG repeat length and are found to have an expansion greater than 35 repeats are considered HD expansion carriers. They have the gene for the disease, but they show no current signs or symptoms.

HD Prodrome: The prodrome of HD is a new phase that have been observed by detection and characterization of certain cognitive and behavioral symptoms that are at risk in persons who are years from the appearance of motor symptoms that are currently used for clinical diagnosis of HD. Medical dictionaries define a prodrome as a clinical or physiological indicator that precedes the onset of the disease. The prodrome may appear up to 15 years before the onset of the motor symptoms.

- **HD Prodrome A:** The prodromal phase of HD can be said to begin when any sign or symptom of HD is noted in a person in the HD at risk or HD Expansion Carrier groups. In studies, that separate the prodrome into two groups, this phase is referred to as pre-HD A. This phase suggest that slight volume loss has begun, with the most prominent changes in the basal ganglia. The rate of volume loss over time is about 4% per year. Motor ratings can vary widely in this phase, with most having few or no motors symptoms as some showing motors abnormalities that are inconsistent or not yet severe enough to warrant a diagnosis.

➢ Fatigue is likely to be present.
➢ Emotion recognition may become impaired.
➢ Mood, anxiety and obsessive thinking may all be mildly elevated.
➢ Progression in this phase is very slow and rarely noticeable.

- **HD Prodrome B:** The prodrome phase having “medium probability of diagnosis within 5 years” (60-85%) or being at the “midpoint towards motor diagnosis” (7-13 years) is typically the phase with the most variation in disease presentation. There appears to be a point in time when HD takes over, accelerates or become more aggressive and it seems to occur 8 to 15 years prior to receiving a motor diagnosis. As a result, some persons in this phase are beginning the more rapid progression seen in HD prodrome C phase and some continue to progress slowly and more similarly to those in the HD prodrome A phase.
- **HD Prodrome C:** The prodrome phase referred to as “high probability of diagnosis within 5 years” (>85%) and “near motor diagnosis” (<7 years) is the phase with the most pronounced rate of decline in all area studied. This phase is the one that should be used for testing new treatments, since change over time is significant and the measurement of every domain (motor, cognitive, MRI scan) is robust due to advancing disease. MRI volume changes are over 4% per year and the chanfs in cognitive and motor scores are great.[56]

Clinical Stages of HD

HD diagnosed stage 1(0 to 8 years since motor diagnosis): Maintains only marginal engagement in occupation having part time voluntary for salaried employment potential and maintains typical pre-disease levels of independence in all other basic functions such as financial management domestic responsibilities and activities of daily life(eating, dressing, bathing etc.) or satisfactorily in typical salaried employment(perhaps at a lower level) and requires slight assistance in only you basic functions that is finances, domestic chores, or activities of daily life.

HD diagnosed stage II (3-13 years since motor diagnosis) : Typically unable to work, requiring only slight assistance in all basic functions: Finance, domestic, daily activities; or enable to work and requiring different levels of assistance with basic functions (some are still handled independently).

HD diagnosed stage III (5-6 years since motor diagnosis): unable to engage in employment and requires major assistance in basic functions: financial affairs, domestic responsibilities, and activities of daily living.

HD diagnosed stage IV (9-21 years since motor diagnosis): requires major assistance in financial affairs, domestic responsibilities, and most of the activities of daily living. For example, comprehension of the nature and purpose of procedures may be intact, but a major assistance is required to act on them. Care may be provided at home but needs may be better provided at an extended care facility.

HD diagnosed stage V (11-26 years since motor diagnosis): Requires major assistance in financial affairs, domestic responsibilities, and all activities of daily living. Full time skilled nursing care skilled nursing care is required.[57]

Epidemiology

Huntington's disease is a rare neuropsychiatric disorder with a prevalence of 5-10 per 100,000 in the Caucasian population.[58] The prevalence of the clinical syndrome is 37:100,000 whereas nearly 20:10,000are carriers of the gene responsible for the disease.[59]

HD is currently found in many different countries and ethnic groups around the world. There are varying rates of prevalence in different racial groups. The highest frequencies of HD are found in Europe and countries of European origin. The lowest frequency of HD is

documented in Africa, China Japan and Finland. The frequency of HD in different countries varies greatly. The few isolated populations of Western European origin have an unusually high prevalence of HD. These include the Lake Maracaibo region in Venezuela (700 per 100,000), the islands of Mauritius off the South African coast (46 per 100,000 people0 and Tasmania (17.4 per 100,000 people). The prevalence in most European countries ranges from1.63-9.95 per 100,000 people. Studies on the distribution of CAG repeats in the normal population suggest a higher prevalence of HD in India closer to that seen in Western Europe.[60]

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.[61, 62]

Etiology

Huntington's disease is an autosomal dominantly inherited disease caused by an elongated CAG repeat on the short arm of chromosome 4p16.3 in the Huntingtin gene.[92] This gene codes for the huntingtin protein and, on exon 1, contains the CAG tract. The wild-type contains a CAG repeat, coding for a polyglutamine stretch in the protein at that site in the range 6 to 26.

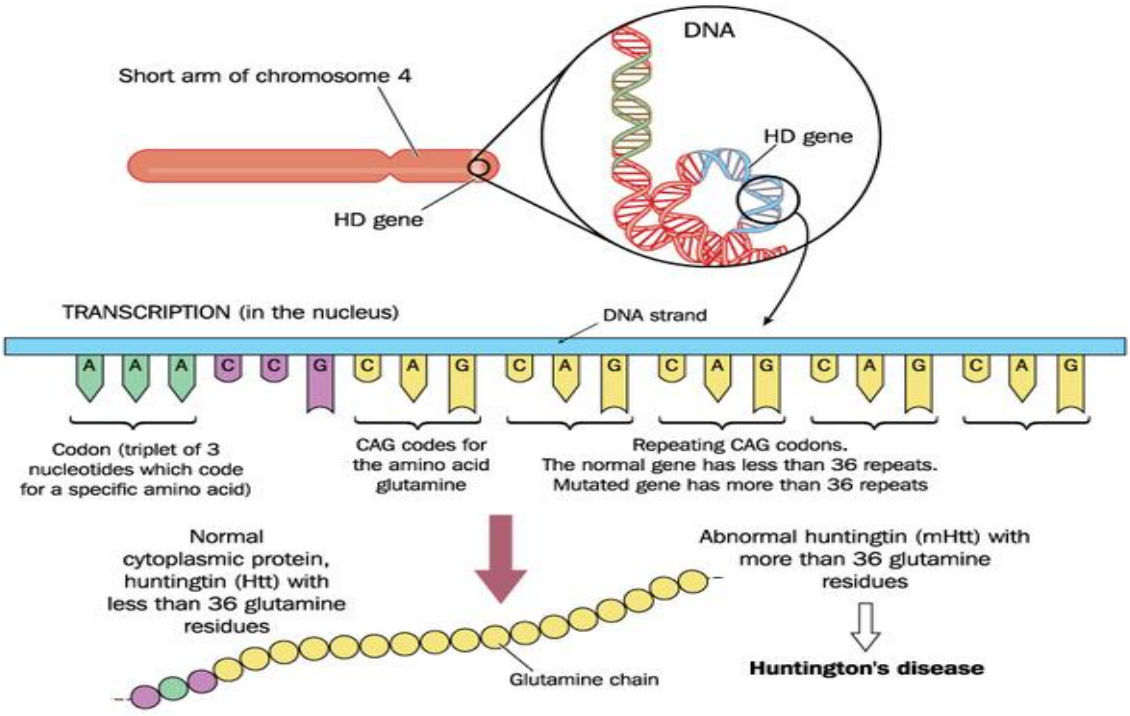

Figure 3: Genetics of Huntington Disease.

Huntington's disease is associated with 36 repeats or more. Definite clinical manifestation will occur if the number of repeats exceeds 40. The range 36-39 leads to an incomplete penetrance of the disease or to a very late onset. The range between 29 and 35, the so-called intermediate alleles, is unstable, which means that these alleles are prone to changes during reproduction. Copying the gene may lead to mistakes and very often leads to elongation and seldom to shortening. This phenomenon is mainly seen in the male line of reproduction.[93]

An inverse correlation has been described between the length of the repeat and the age at onset, determined by the first motor manifestation. The longer the CAG repeat, the earlier the onset. When the disease starts before the age of 20 years, so-called juvenile Huntington's disease (JHD), the repeat often exceeds 55.[94] The length of the repeat determines about 70% of the variance in age at onset and gives no indication at all about the initial symptom, the course, or the duration of illness. The only correlation now described is the faster weight loss associated with a longer CAG repeat.[95] Anticipation phenomenon is seen in Huntington families in the paternal line of inheritance.

The normal wild-type Huntingtin protein plays a role in synaptic function, is necessary in the post-embryonic period, possibly has an anti-apoptotic function and is possibly protective against the toxic mutant, huntingtin.[96] There is evidence that the mutant form leads to a gain of function as well as to a loss of function. The role of the mutation has been studied in many models: cells, fibroblasts, C. Elegans, drosophila, mice, rat, sheep and monkey. Mice models (more than 10 available) are most commonly used. As neuronal intranuclear and intracytoplasmic inclusions are found, it is still not clear what role they play. Are the inclusions pathogenic in themselves or are they only a side-product of other mechanisms? The inclusions are present in many areas of the brain. The overall pathology, brain atrophy, particularly in the striatum with extensive neuronal loss, is well known.[97, 98]

Pathophysiology

The part of the brain most affected by HD is a group of nerve cells at the base of the brain collectively known as the basal ganglia. The basal ganglia organize muscle-driven movements of the body, or "motor movements". The major components of the basal ganglia are the caudate and the putamen (together known as the Striatum) and the globus pallidus (external and internal regions). The clinical symptoms of HD reflect the pattern and the extent of neural loss within different components the basal ganglia-thalamocortical circuit. The neostratum (caudate nucleus and putamen) receives excitatory glutamatergic inputs from

the entire neocortex, the first step in the anatomical loop responsible for the initiation and execution of movement.[63]

HD disease interacts with the two proteins and huntintong's interactor protein (HIP-1) and Huntington's associated protein (HAP-1). These two proteins are present in the brain. The striatum is composed of a variety of medium to large neurons that differ in their size and dendritic profile as well as neurochemical content and output. Medium spiny neurons are inhibitory projection neurons carrying the output of the striatum to the globus pallidus and the substantia nigra and are the major neuronal type, comprising approximately 95% of the neuronal cell in the striatum.[64]

Neuropathology

Neuropathological changes in Huntington's disease are strikingly selective, with prominent cell loss and atrophy in the caudate and putamen.[65-67] Striatal medium spiny neurons 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.[68, 69] 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.[70]

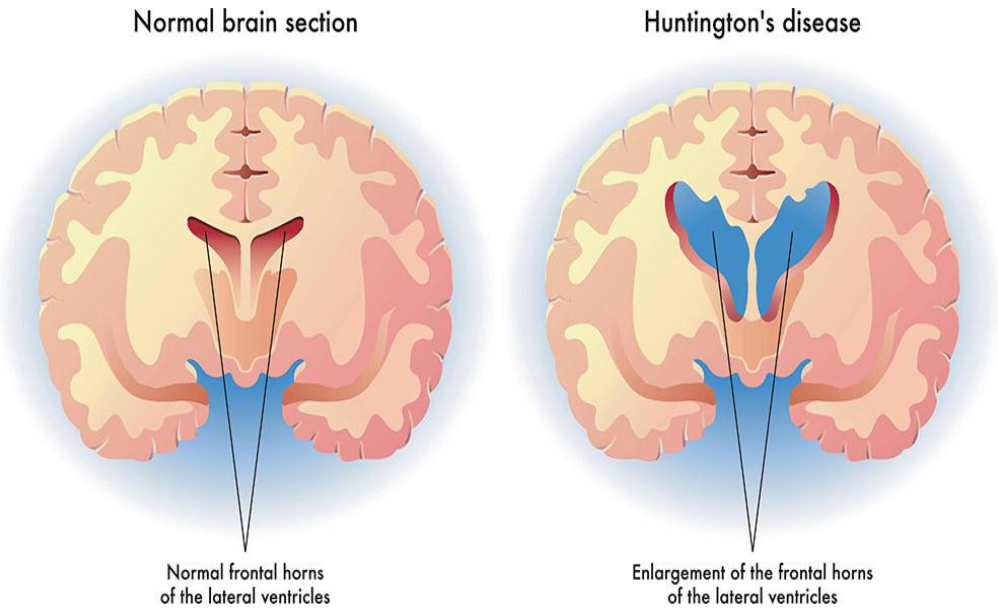

Figure 4: Effect of HD on Brain.

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[71], the angular gyrus in

the parietal lobe[72,73], Purkinje cells of the cerebel[74], lateral tuberal nuclei of the hypothalamus[75,76], and the centromedialparafascicular complex of the thalamus.[77]

In early symptomatic stages of Huntington's disease, the brain could be free of neurodegeneration.[78-80] However, evidence of neuronal dysfunction is abundant, even in asymptomatic individuals. Cortical neurons show decreased staining of nerve fibres, neuro-fi laments, tubulin, and microtubule-associated protein 2 and diminished complexin 2 concentrations.[81,82] 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 polyglutamin.[83] Although indicative of pathological poly glutamine processing, and apparent in affected individuals long before symptom onset[84], 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.[85]

In some transgenic mouse models of Huntington's disease, inclusions arise only after symptoms begin.[86] Cells that have inclusions seem to survive longer than those without[87], and little correlation is seen between the various cellular and animal models of the disorder and human Huntington's disease, in terms of the appearance of inclusions in histopathological specimens and the onset of dysfunction or neurological symptoms.[84, 87, 88-90] A compound that enhances aggregate formation might actually lessen neuronal pathological findings.[91]

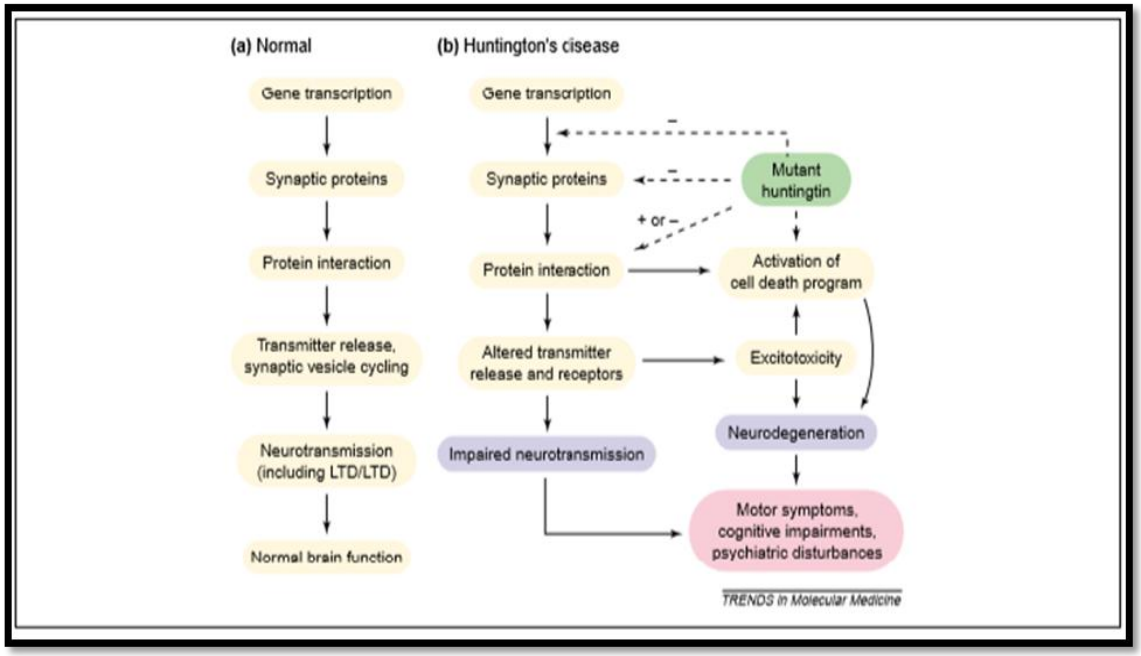

Figure 5: Principal cellular processes involved in the regulation of synaptic transmission. (a) Regulation under normal conditions. (b) Regulation under the pathological influences of mutant huntingtin. The most important take-home message is that not only does mutant huntingtin cause cell death directly, but also it can impair synaptic transmission at several levels, thereby leading to symptoms.

Signs and Symptoms of Huntington's Disease

The nuclear symptoms and signs of Huntington's disease (HD) consist of motor, cognitive and psychiatric disturbances. Other less well-known, but prevalent and often debilitating features of HD include unintended weight loss, sleep- and circadian rhythm disturbances and autonomic nervous system dysfunction. The mean age at onset is between 30 and 50 years, with a range of 2 to 85 years. The mean duration of the disease is 17-20 years. The progression of the disease leads to more dependency in daily life and finally death. The most common cause of death is pneumonia, followed by suicide.

The motor symptoms and signs

The characteristic motor changes are involuntary, unwanted movements. Initially, the movements often occur in the distal extremities such as fingers and toes, but also in small facial muscles. For bystanders these muscle twitches are often invisible or can be explained as nervousness. In daily life, walking becomes unstable and the person can look as if he/she is slightly drunk. Gradually the unwanted movements spread to all other muscles from distal to more proximal and axial. Choreatic movements are present all the time the patient is awake.

No single pattern exists, but facial choreatic movements can lead to a continuous movement of facial muscles where for instance an eyebrow is lifted, an eye closed, the head is bent or turned while the tongue is protruded with the lips pouting. The most prominent are the extension movements of the long back muscles. Talking and swallowing gradually become more problematic leading to choking at any time in some patients.

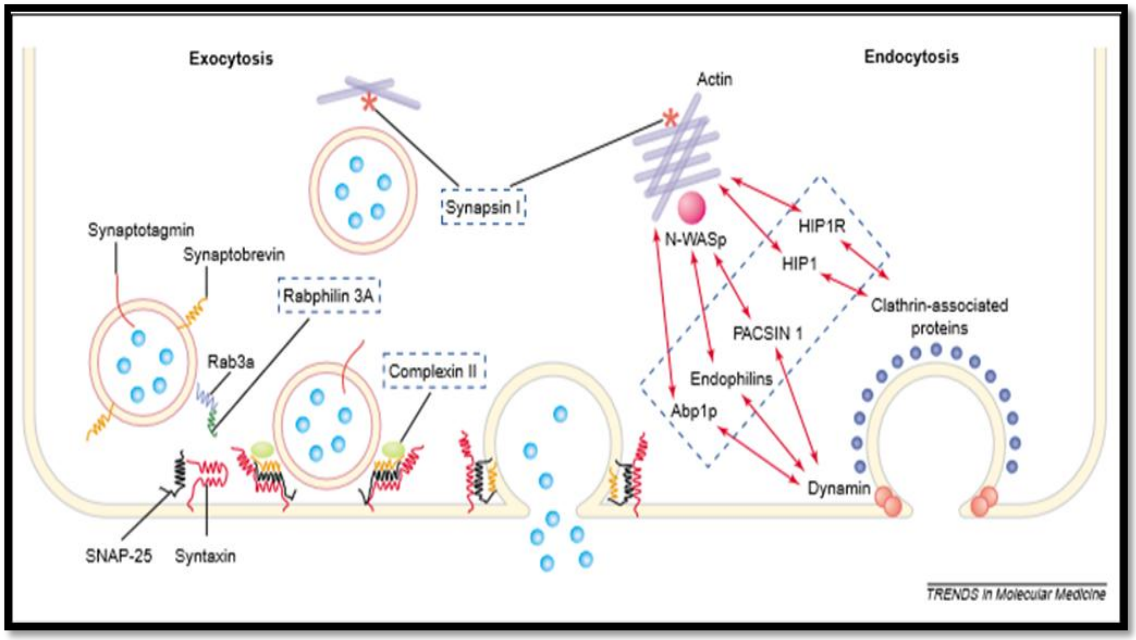

Figure 6: Protein–protein interactions among key factors involved in exocytosis and endocytosis. Red arrows between individual proteins indicate specific binding interactions between those components. Dashed blue boxes indicate protein–protein interactions that potentially could be altered by mutant huntingtin, thereby disturbing endocytosis and exocytosis. Abbreviations: HIP1, Huntingtin-interacting protein 1; HIP1R, HIP1-related protein; N-WASp, neuronal Wiskott–Aldrich syndrome protein; PACSIN 1, protein kinase C and casein kinase in neuron.

In later stages the patient even becomes mute. Dysarthria and dysphagia become very prominent during the course of the disease. All patients develop hypokinesia, akinesia, and rigidity leading to a slower pace of all activities (bradykinesia: slowness of movement) and a severe hesitation in embarking on a movement (akinesia: difficulty in starting movements)). The balance between chorea and hypokinesia is determined individually. The extremes are on the one hand the younger patient with an overwhelming rigidity (Westphal variant) and on the other hand the very old patient severely affected in the last stage of the disease with a long duration of illness, bed-bound with rigidity and flexion contractures in the extremities.

Dystonia is characterized by slower movements with an increased muscle tone leading to abnormal posture, for instance torticollis, but also rotation of the trunk or limbs. Dystonia (for instance torticollis) can be the first motor sign in Huntington's disease. Other unwanted movements include tics, comparable to the ones seen in Tourette syndrome, but these are fairly rare. Cerebellar signs can appear sporadically, similar to the presence of hypo- and hypermetria.

Walking is often described as 'drunk' or 'cerebellar ataxia'-like. Distinguishing between choreatic and ataxic walking is very difficult. Pyramidal signs (Babinski sign) are present incidentally.

The influence of motor disturbance on activities of daily life progresses over time. The presence of hyperkinesia and hyperkinesia results in difficulties in walking and standing, and frequently leads to an ataxic gait and frequent falls. Furthermore, daily activities such as getting out of bed, taking a shower, and dressing, toileting, cleaning the house, cooking and eating become more and more difficult. Depending on the kind of work the patient does, motor signs will sooner or later interfere with performance, even if psychiatric and cognitive changes are still in the background.

Behavior and psychiatric symptoms and signs

Psychiatric symptoms are very frequently present in the early stage of the disease, often prior to the onset of motor symptoms. The percentage of patients with psychiatric signs varies between 33% and 76% depending on the methodology of the study.[99] Because of their impact on daily life, these symptoms and signs usually have a highly negative impact on functioning and on the family.[100] The most frequently occurring sign is depression. The diagnosis is difficult because weight loss, apathy and inactivity also occur in HD. Usually there is low self-esteem, feelings of guilt and anxiety. Apathy is related to disease stage, whereas anxiety and depression are not. Suicide occurs more frequently in early symptomatic individuals and also in premanifest gene carriers. Around the time of the gene test and the stage when independence diminishes are the most risky periods for suicide.

Figure 7: Signs and symptoms of HD.

Anxiety also occurs frequently (34-61%), sometimes in relation to uncertainty about the start and or the course of the disease. Obsessions and compulsions can disturb the patient's life and also lead to irritability and aggression. Irritability is often the very first sign, in retrospect, but in fact occurs during all stages of the disease.[99] The way irritability is expressed varies enormously from serious disputes to physical aggression. A loss of interest and increasing passive behaviour are seen as part of the apathy syndrome. It can be difficult to discriminate apathy from depression. Pychosis may appear, mainly in the later stages of the disease. In most cases this goes together with cognitive decline. The complete clinical picture is comparable to schizophrenia with paranoid and acoustic hallucinations. In the early stages, hypersexuality can cause considerable problems in a relationship. In the later stages hypo-sexuality is the rule.

Dementia

Cognitive decline is the other main sign of HD and can be present long before the first motor symptoms appear, but can also be very mild in far advanced stages of the disease. The cognitive changes are particularly in relation to executive functions. In normal conditions, cognitive and motor behavior is goal-directed and planned. Normally individuals are able to distinguish what is relevant and what can be ignored, but patients with HD lose this capability. The patients are no longer able to organize their life or to plan things which in the past were simple.

They lose flexibility of mind, and can no longer make mental adjustments. Misjudgments lead to complicated situations, with patients no longer reacting as they did in the past or in a

way that the environment expects. Language is relatively spared. Memory certainly becomes impaired, although the semantic memory can be spared to a certain extent. All psychomotor processes become severely retarded.[101]

Secondary symptoms and signs: From early on, an unintended weight loss has been reported in all patients. As more attention is now paid to this phenomenon, the loss seems to be a little less severe, the cause being diverse. Although it seems logical to think that chorea should play the main role in weight loss, it has been shown that there is no relation between weight loss and chorea or other movement disorders. A relation with the length of the CAG repeat has been described.[102] More practical issues, such as slower functioning, decreased appetite, difficulty handling food and swallowing certainly play a role. But hypothalamic neuronal loss is also a causative factor.[103,104]

Attention has only recently been focused on sleep and circadian rhythm disturbances of patients with HD.[105] Autonomic disturbances can result in attacks of profuse sweating.[106]

DIAGNOSIS

The diagnosis is based on the clinical symptoms and signs in a person with a parent with proven HD. First, it is obligatory to take a precise history from the person with symptoms followed by a detailed family history. When all information has been obtained the diagnosis is not very difficult, although non-specific clinical pictures can be misleading.

Also when the parent is not known or has died due to another cause at a young age, the clinical picture can be difficult to recognize. It is often necessary to request old information in the form of medical records and autopsy reports. The current gold standard is DNA determination, showing a CAG-repeat of at least 36 on the huntingtin gene on chromosome 4.

Before 1993, a family history with clinical and morphological verification in at least one of the parents or grandparents was obligatory. The clinical criteria currently necessary are still motor changes with or without psychiatric or cognitive changes. However, in most cases a combination of the three main signs is present. The combination with the family history is sufficient for diagnosis. No imaging, general blood tests or other diagnostic tools are helpful. For all diagnostic tests, it is necessary to obtain informed consent from the patient.

This is important because if that person is given a diagnosis of Huntington's disease, then probably many more individuals around the patient will be confronted with an increased risk

of Huntington's disease. Extensive studies are underway to detect biomarkers (clinical, blood, MRI) and hence the transition determining parameters.[107] Several studies are now focussing on changes in function and changes in brain imaging (MRI) before clinical overt manifestation is present. It seems that brain volume and brain connections show changes several years before any clinical manifestation is present.[108]

Differential Diagnosis

When chorea is the presenting and most prominent sign, taking a history is the first and most valuable step. The frequently occurring differential diagnoses for motor sign chorea are given in Table 5.1. In many cases the underlying cause is another general internal disorder or an iatrogenic disorder. Only very few genetically determined disorders are responsible for choreatic syndromes. In about 1% of the cases clinically diagnosed as HD by the clinician, the genetic test.

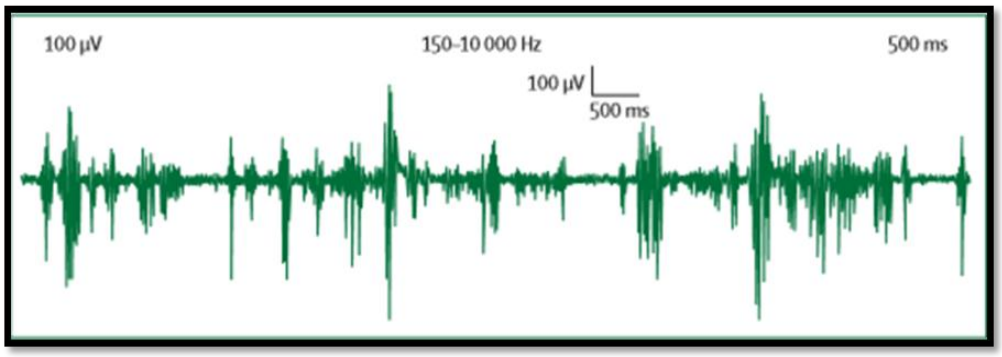

Figure 8: EMG recording of chorea in patient with stage I Huntington's disease Recording is made with standard belly tendon using surface disc electrodes placed over the first dorsal interosseus muscle. Note the irregular pattern of discharges, with variable amplitude, duration, and rise times of every EMG burst. Healthy individuals at rest show no EMG activity.

Does not confirm the diagnosis. These are the so-called phenocopies.[109] Phenocopies are defined by a clinical diagnosis of HD with chorea, psychiatric and or cognitive signs and an autosomal dominant pattern of inheritance or family history. In the last few years, several have been described.[110]

Genetic Counseling

When the gene was localized on chromosome 4 in 1983[111], premanifest diagnosis became available for the first time using linkage analysis. Linkage analysis provided the applicant

with results, initially with a certainty of 93% and later with a certainty of about 98%. When in 1993 the CAG repeat on chromosome 4 was described, real premanifest diagnosis could be given to those at risk of HD.

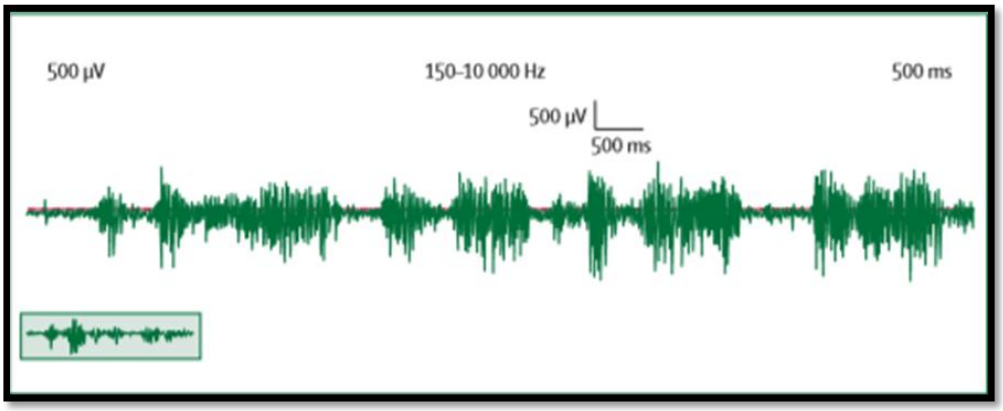

Figure 9: EMG recording of motor impersistence. The patient is instructed to maximally abduct the second digit against resistance and to maintain it. Note that motor activity fades repeatedly. The parenthetical inclusion is a copy of the first 400 ms of resting chorea shown in figure 5.1. a, adjusted for the diff erent amplitude settings, for comparison. Note that choreiform bursts intermittently exceed the EMG activity from maximum volitional effort. Healthy individuals show consistent EMG amplitude during this task.

It was the first disease in which this technique became practically available, functioning as an example of how to cope with new questions and problems. A manifest was written by the HD community, a collaboration of scientists, doctors and lay people.[112] The standard procedure was the following: step 1, consultation with a clinical geneticist and preferably in combination with a psychologist and a neurologist. After 4-6 weeks a second consultation (step 2) takes place including blood sampling.

Table 2: Differential Diagnosis for chorea.

Hereditary	**-Huntington's disease**
	-Benign hereditary chorea
	- Neuroacanthocytosis
	-DentatoRubroPallidoLuysianAtrophy (DRPLA)
	- Wilson disease
Rheumatic disorders	- Sydenham chorea
	- Chorea gravidarum
Drug-induced	- Neuroleptic drugs
	- Oral anticonceptive drugs

	- Phenytoine
	- Levo-dopa
	- Cocaine
Systemic disorders	- Systemic Lupus Erythematodes (SLE
	- Thyrotoxicosis
	- Polycythemia vera
	- Hyperglycemia
	- Paraneoplastic

After a period of 68 weeks a consultation (step 3) with disclosure is planned. Exclusion criteria for the procedure are: age below 18 years, severe psychiatric illness, and external pressure for the applicant. Long discussions took place concerning applicants with a 25% risk at the time of the request. The procedure was extended with the rule that maximal efforts must be taken by the applicant to get a result from the parent with a 50% risk of HD. Finally the 25% at risk applicant can get his test.[113]

Prenatal diagnosis

As the test can be performed on any cell with a nucleus containing DNA, antenatal diagnosis is also possible. Between the 10th and 12th weeks of pregnancy, chorionic villus sampling and between the 15th and 17th weeks amniocentesis can be performed and DNA-testing carried out. The procedure is only initiated if the parents already know their own genetic status to prevent unwanted disclosure for two individuals at the same time. The procedure is embarked on with the intention of ending the pregnancy if the HD gene is found in the embryo. The mother cannot be forced to agree with this conclusion.

If the parents have not yet been genotyped, one can opt for an exclusion test by comparing the genetic status of the embryo with that of the grandparents. In this situation the result is either 0% risk for the foetus, and so the parent keeps his or her 50% status, or 50% risk for the foetus. The foetus has received a chromosome from the affected grandparent, but it is not known to which chromosome the HD gen is coupled. In this case the foetus has a 50% risk, comparable to the parent, and the parents can decide to abort a 50% at risk baby.

Table 3: Phenocopy of Huntington's disease (OMIM).[114]

	Mutation	Locus
1. HDL1	octapeptiderepeatexpansion PRNP-gen	20pter.p12
2. HDL2	CTG/CAG-expansion JPH3-gen	16q24.3
3. HDL3	Not known	4p15.3
4. SCA17 (HDL4)	CAG/CAA-expansion TBP-gen	6q27
5. SCA1/2/3	CAG-expansion ATXN1/2/3-gen	6p23, 12q24, 14q24-q31
6. DRPLA	CAG-expansion ATN1-gen	12p13
7. Chorea-acanthocytosis	mutation VPS13A-gen	9q
8. McLeod syndrome	mutation XK-gen	Xp21.2-21.1
9. NBIA2	mutation PLA2G6-gen	22q13.1
10. NBIA1/PKAN	mutation PANK2-gen	20p13-12.3
11. Friedreich ataxia	GAA-expansion FXN-gen	9q13; 9p23-p11

HDL = Huntington Disease-Like; SCA = Spinocerebellar ataxia; DRPLA = Dentato Rubro Pallido Luysian Atrophy; NBIA = Neurodegeneration with Brain Iron

Accumulation; PKAN = Pantothenate-Kinase-Associated-Neurodegeneration

During the last decade, preimplantation diagnostics has also been offered in several countries. The procedure starts with in vitro fertilization. When the embryo is in its eight-cell stage, one cell is removed for DNA testing. The embryo without the elongated CAG repeat is placed in the mother's womb to allow a normal pregnancy to develop. Before starting this procedure, the genetic status of the parent must be known, although not all countries follow this line of thinking.[115]

Symptomatic Treatment of Huntington's Disease

Many therapeutic options are available for treating symptoms and signs with a view to improving quality of life. Although many signs and symptoms can be treated, it is not always necessary to do so. The patient's limitations in daily life determine whether or not drugs are required. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms. Drug treatment is, therefore, individualized and based on expert opinion and daily practice.

Treatment consists of drug prescription and non-medication advice. Surgical treatment does not play an important role in HD.[116,117]

Chorea

Chorea is characterized by abnormal, involuntary, spontaneous, uncontrollable, irregular, intermittent, non-rhythmic and aimless movements affecting the trunk, the face, and the limbs. Drug treatment should be considered if chorea causes the patient distress or

discomfort. Tetrabenazine is one of the first-line treatments for this symptom[118] unless the patient suffers from not well-managed depression or suicidal thoughts. Second generation neuroleptics[119,120] are first-line treatments for this symptom in particular when the patients have associated personality and/or behavioral or psychotic disorders. Monotherapy to treat chorea is preferred because combination therapy increases the risk of adverse effects and may complicate the management of non-motor symptoms. In the presence of disturbing chorea, appropriate protective measures (especially during meal times and during the performance of instrumental activities of daily living) should be put in place to avoid traumatic injury or chokes. Rehabilitation specialists can help identify appropriate assistive technology devices and positioning techniques.

Table 4: Drug treatment for chorea.

Tiapride	**max 600 mg**
Olanzapine	max 20 mg
Tetrabenazine*	max 200 mg
Pimozide	max 6 mg
Risperidone	max 16 mg
Fluphenazine	max 10 mg

***When tetrabenazine is officially approved per country, this drug will probably become the drug of first choice based on the literature.**

Dystonia

Dystonia is characterized by abnormal postures that may affect all body segments and is frequently associated with rigidity.[121] Dystonia intensity varies from a slight intermittent abnormal posture to severe twitch of muscles with major impact on movements and functions of daily living. Both active and passive physiotherapy approaches are recommended as a preventive measure to maintain the range of joint motion, limit postural and musculoskeletal deformities and, prevent the development of contractures. Injection of botulinum toxin in the case of focal dystonia or to prevent secondary deformities should be performed by a trained professional. Customized chairs can provide a comfortable environment in view of the dystonia-related deformities.

Rigidity

Rigidity is an increase in muscle tone leading to a resistance to passive movement that can induce joint stiffness and limited range of motion, which might be distressing for patients. Rigidity may be increased or induced by the use of neuroleptics or tetrabenazine. If this

impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered considering overall benefit on chorea and/or behavioral symptoms vs. severity of rigidity. Levodopa may provide partial and temporary relief of the akinetic–rigid symptoms of HD, especially in juvenile forms.[122-127] Treatment with levodopa should be started gradually and the total daily dose is usually lower than in Parkinson's disease. Physiotherapy is recommended to improve or maintain mobility and prevent the development of contractures and joint deformity.[128]

Akathisia

Akathisia is a syndrome characterized by unpleasant sensations of "inner" restlessness that manifests as an inability to sit still. An iatrogenic cause of akathisia should be investigated as the priority. Tetrabenazine[129,130], neuroleptics and Selective serotonin reuptake inhibitors (SSRI) may cause akathisia in HD and reducing the dose or changing the treatment may be helpful.

Swallowing Disorders

Swallowing disorders can occur in patients at the early stages of the disease and become a major problem in later stages by inducing repeated choking and leading to secondary bronchopulmonary infections or even cardiac arrest. Regular assessment of swallowing disorders should be provided throughout the progression of the disease[131] and referral to a Speech and Language Therapist is recommended as soon as the disorders appear.[131-133]

Ancillary assessments that may help in managing swallowing disorders include: generalized motor skills, respiratory status, dental health, mood, behavior and emotional status, cognition, nutrition, and hydration status. Provision of information and advice on safe swallowing procedures, on posture and positional changes can help to avoid aspirations and leads to improvement of swallowing disorders. Oral-facial exercise with swallow sequence individualization and cough post swallow may also improve swallowing difficulties. In some cases, treating chorea might help in improving swallowing problems. However, side effects of treatments for chorea (e.g., sedation, attention, and parkinsonism) might also negatively impact swallowing capacities.

The education of carers is important as they are often managing the eating, drinking, and swallowing regime.

For severe swallowing disorders impacting nutrition and quality of life of the patient, the use of a gastrostomy device Percutanous Endoscopic Gastrostomy (PEG) may be considered and should be discussed on a case-by-case basis with the patient and the caregivers.

PEG should be anticipated and discussed with relatives and patients still able to understand the benefits and burdens of the methods. Before advanced stages of the disease, patients should be educated to make an informed choice concerning the PEG methods even if they can change their decision at any time.

Myoclonus

Myoclonus refers to sudden muscle contractions, brief and involuntary, axial, in extremities or generalized, similar to spams and jerks in epileptic seizures but not related epilepsy. In HD, myoclonus can be observed in a predominant akineto-rigid phenotype and can be associated with an at rest or action tremor, especially in the juvenile forms but also in later-onset forms. In juvenile forms, non-epileptic myoclonus can coexist with epilepsy.

In case of myoclonus impacting the functional capacity of the patients, treatment with sodium valproate or clonazepam, used alone or in combination, and in escalating doses, is recommended.[134-141] Levetiracetam is a therapeutic alternative for the same indication. In case of myoclonus of cortical origin that is not associated with epileptic seizures, piracetam has a marketing authorization.[138] Benzodiazepines, in particular clonazepam, may be used to manage myoclonus whilst remaining vigilant with regard to adverse effects such as somnolence and increasing falls, and the risk of drug-dependence.

Gait and Balance Disorders

Gait and balance disorders impairments include disruption of cadence regulation, increased variability of step width and length, disturbed initiation and increased postural sway.[142] These develop as a result of the progressive complex movement disorder seen in HD adding to the overall burden of motor morbidity with falls and loss of independence in HD.[143]

Generally, interventions for gait and balance should start as early as possible and be continued and adapted throughout the progression of the disease.[142, 144-147] Physiotherapy interventions[148-151] and the introduction of falls prevention programs, gait, core stability, and balance interventions[144, 152-154]as well as attention training are recommended.

Pharmaceutical management of chorea may improve walking and balance as they can be affected by chorea.[155-158] However, they should always be used cautiously and regularly reassessed as their adverse effects may also aggravate walking disorders. Maintaining physical activity and low impact exercises is recommended. The use of assistive devices such as four-wheeled walker[159] as recommended by Physiotherapist or Occupational Therapist should be considered to improve stability and reduce fall risk.

Bruxism

Bruxism is an involuntary clenching with excessive contraction of the jaw muscles. It typically causes lateral movements (or front to back) responsible for gnashing and can lead to tooth damage.

Injecting botulin toxin A into the masseter muscles is proposed as the first-line treatment of bruxism.[160] Customized protective mouth guards may be used to reduce the complications of bruxism on a case-by-case basis, mostly in early stage patients.

Bruxism may occur as a side effect of neuroleptics[160;161] and serotonin reuptake inhibitors, thus reducing their dose should be considered.

Manual Dexterity

Manual dexterity can be impaired secondary to chorea/dystonia/akinesia/rigidity but also occur in their absence—due to abnormal motor planning and sequencing.

Neuroleptics and tetrabenazine may possibly have a beneficial effect on dexterity as a result of reducing chorea[155,156,162] but may also have a detrimental effect on dexterity by aggravating other symptoms such as bradykinesia.

Management with physiotherapy and occupational therapy may be useful to reduce the functional impact of fine motor skill deterioration.[149] Adaptive aids may help to compensate for the deterioration of manual dexterity.

Global Motor Capacities

Early referral to a physiotherapist is recommended in order to facilitate the development of a therapeutic relationship, promote sustainable exercise behaviors and ensure long-term functional independence.

Physiotherapy and/or personalized exercise programs[148] are beneficial for the overall functional ability, motor function, and independence in HD, in combination with pharmacological treatments.[148,150, 151]

Cognitive Disorders

Cognitive deficits appear frequently before motor symptoms.[163] They are, in addition to behavioral symptoms, the major cause of family disruption and social withdrawal.[164] Cognitive symptoms cause intense psychological discomfort and a sense of powerlessness that can lead to behavioral symptoms.

Based on present knowledge, no pharmacological treatment is recommended for the treatment of cognitive symptoms.

Multiple rehabilitation strategies (speech therapy, occupational therapy, cognitive and psychomotricity) might improve or stabilize transitorily cognitive functions at some point of time in the course of the disease.[165]

Executive Functions

Executive functions refer to the functions that allow the realization of complex task in daily living. They consist in a set of functions mostly dedicated to cognitive and behavior control and adaptation, which may be impaired in HD, even at the premanifest stages and thus impose adaptation from the environment, organization support including proactivity in planning appointments, behavior or daily life activities like cooking. For the patients to maintain their independence for as long as possible, it is better to help the patients organize themselves and initiate activities rather than substitute for them, as long as they do not endanger themselves.

Treatment for anxiety and depression may help to improve executive function and cognitive stimulation through rehabilitation may improve planning and initiation more specifically.[166] Sedative drugs and neuroleptics should be closely monitored as they impair executive functions and attention.

Bradyphrenia

Bradyphrenia is defined by slowing of cognitive information processing and a prolongation of reaction time depending on the complexity of the cognitive task.[167] It becomes more apparent with HD disease progression. Management is based on giving the patient enough time to process information and perform a task and avoiding time-pressured situations. Cognitive stimulation as part of rehabilitation may be beneficial.

Language and Communication Disorders

Language and communication disorders can be divided in speech and language disorders per se. Speech disorders consist of slurred and slowed speech causing dysarthria, inappropriate

pauses or bursts of speech, and progressive reduction in verbal fluency.[168] Language (e.g., syntax) impairments appears early in the disease course, with progressive difficulties in understanding and producing complex sentences. Reduction of lexical capacities appears later. This often goes unnoticed and may cause misunderstanding and impaired communication.

The changing communication needs of the person with HD should be reassessed throughout the course of the disease to plan effective management strategies. As communication disorder in HD is variable, its monitoring requires comprehensive assessment of language and of other factors such as mood, motivation, and behavior. Early referral to Speech and Language Therapists is recommended[169] as they can play a major role in assessing and managing communication problems in HD at all stages of the disease.

Communication strategies and techniques may include: management options(e.g.,voicetherapy techniques), advice on facilitation of communication (e.g., allowing time for communication, reduction of environmental distractions and noise) and the use of simple technics (e.g., gestures and rephrasing) or tools (e.g., pen and phones). Family members and other communication partners should be educated to support patients to attempt verbal communication as long as possible. Augmentative and alternative communication (talking mats) can compensate for communication difficulties and increase the individual's chance of participation in daily life. These strategies need to be implemented whilst there is still motivation and a capacity to learn.[170]

Social Cognition Impairments

Social cognition impairments refer to a set of symptoms that affect relationships and social behavior. The most studied are the inability to recognize emotion, others but also to express emotions, both through facial expression or through the voice. Executive function impairments can make difficult for the patients to express their feelings. The capacity to infer other thoughts or feeling, are also reported to be impaired in patients.[171] Furthermore, motor impairment scan create a "facial mask," often misunderstood as indifference.

Improvement of behavioral disorders may help with social and family integration. However, impact of SSRI or neuroleptics on social interaction *per se* has not yet been properly assessed to allow any recommendation specific to this domain. Explaining the patients' disorders to their family, health care professionals or to their colleagues may facilitate the patient's social

relationships. Moreover, third party intervention (e.g., caregiver, nurse, and social worker) may stimulate patients' social interaction.

Memory Disorders

Memory disorders are frequently reported in HD and may be confounded with or exacerbated by attention disorders. They are mostly characterized by difficulties in learning new information and retrieving information acquired.[172] Strategies such as establishing and keeping a regular daily routine may compensate memory loss.

Rehabilitative approaches (speech therapy or neuropsychology) may help memory as part of an overall intervention plan. Specifically, domain-specific transcoding (verbal and visual) may help in recalling items. Sedative drugs, neuroleptics and tetrabenazine may impact negatively on memory.

Disorientation

Disorientation, both in time and space, appear during the progression of HD but temporal orientation is altered earlier.[173-176]

Investigations should be carried out to detect any potential inter current cause for a confusional state. Establishing a regular routine, in tune with the patient's environment as much as possible, and milestones enables the patient to manage their time better.

Visuospatial and Visual Perceptual Disorders

Visuospatial and visual perceptual disorders appear late in the course of the disease through interference with the integration and understanding of visual information.[176]

It may be useful to make the patient's environment safe (padding furniture) to minimize falls and shocks linked to visual spatial difficulties and aggravated by motor disorders.

Psychiatric Disorders

Behavioral symptoms may appear before the motor diagnosis of the disease. They are, in addition to and in conjunction with cognitive symptoms, the major cause of family disruption, social isolation, and withdrawal.

Their management should be based on the identification of the underlying triggers causing changes in mood or behavior. Patients should be given the opportunity to express their worries and frustrations.

Using methods to calm and reassure patients is a major component of care of psychiatric disorders. Based on data from other neurodegenerative conditions, mindfulness-based cognitive therapy and Acceptance and Commitment Therapy may be useful in HD.

Depression

Depression is one of the most common psychiatric symptoms seen in HD[177,178] with a significant negative impact on quality of life. It may affect patients at any stage of the disease, even before motor manifestation.[179] Thus, vigilance to detect and treat depression is required at all stages of the disease.

Psychotherapy and cognitive behavioral therapy may enable early detection of mood changes. An antidepressant may be suggested if depression occurs in HD.[180] It is recommended to use a selective SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), or alternatively Mianserin or Mirtazapine, in case of sleep disruption. In case of recurrent depression, long-term mood-stabilizer treatment may be introduced in complement to the treatment of the current episode to prevent relapses. If depression is thought to be an adverse effect of other medication, the dosage of the responsible drug should be reduced gradually. In the case of resistant depression, or depression associated with psychotic symptoms, a psychiatrist should be consulted. In case of severe depression and resistant to oral medications, electroconvulsive therapy (ECT) may be suggested under the guidance of a psychiatrist.[181-183]

Suicidal Ideation or Attempts

Suicidal ideation or attempts are common in HD[184] and correlate with family history of suicide, a history of previous suicide attempts and the presence of depression, especially in prodromal stages.[185] Suicide risk should be assessed in HD irrespective of the stage, being particularly vigilant at the time of diagnosis and when the disease starts to impact on day-to-day life. Prevention of suicide includes treating risk factors such as underlying depression, social isolation and impulsivity.

Table 5: Drug Treatment for Depression (A) and Aggression (B).

A. Depression	**B. Agression**
Citatopram- max 6omg	Citalopram-max 60mg
Fluxetine- max 60mg	Sertraline max 200 mg
Mirtazapine- max 45mg	Olanzapine max 20 mg
Valproinezur- max 2000mg	Dipiperon max 360 mg
Carbamazepine- max 1600mg	Haloperidol max 10 mg

(DRUG DOSES VARY INDIVIDUALLY; HERE MAXIMAL DOSES ARE GIVEN; THESE ARE SELDOM NECESSARY IN PRACTICE)

Irritability

Irritability is a very common symptom in HD.[177, 178, 186] This disorder is of fluctuating nature, characterized by impatience and a tendency to become angry in response to minimal provocation. Overflow and loss of control are favored by impulsivity, and can lead to aggressive behavior toward self or others, and rarely, to criminal behavior. This symptom can be caused by the frustrations felt by the patient because of the great loss of his capacities, and by troubles in expressing himself, as well as by neurological/psychological fatigue brought by the latter. Before initiating pharmacological treatment, possible environmental causes for the patient's frustration and irritability should be explored. In order to reduce irritability, behavioral strategies should be considered. A structured plan with a regular routine in a calming environment is desirable. In addition, psycho-education for the patient's family regarding diversion strategies should be attempted to avoid confrontation as much as possible.

Whilst SSRIs are first lines for irritability[187-188], it may be necessary to use them at or near the maximum recommended dose in order to be effective. Irritable patients who do not benefit from an SSRI alone may benefit from combination therapy with Mianserine or Mirtazapine, especially when sleep disorders are present. In patients with aggressive behavior, the recommended first-line treatment is a neuroleptic.[189-191] In case of overt aggression associated with depression, neuroleptic treatment should be associated with sedative antidepressants. If irritability does not respond to antidepressant therapies and/or neuroleptics, a mood stabilizer[192-193] can be added.

Apathy

Apathy has been defined by Levy and Czernecki[194] as "a quantifiable reduction in goal-directed behavior," manifesting clinically as a reduction in interest, spontaneity, motivation, and drive. In patients with HD it is compounded by emotional blunting, resulting in social withdrawal, and lack of concern for others. It is the most frequent psychological and behavioral symptom in HD, especially in the middle and later stages, causing a severe reduction in the activities of daily living and often being a source of conflict in the family.

With regard to cognitive and psychological symptoms, apathy and irritability are the two faces of the same coin.[195] A patient can be apathic the morning and irritable the afternoon,

depending on the situation. As for irritability, apathy can be caused by environmental and psychological issues. Apathy may also be an adaptive response when the patient feels overwhelmed by too much stimulation (HD patients are more sensitive to noise and environmental interferences), or with the feeling that his/her disease is progressing. It is important to explain the various aspects and causes of the apathy to the family circle.

Personalized cognitive stimulation, establishing routines and a structured programme of activities is recommended when possible. A professional intervention at home can improve compliance and reduce the patient's opposition and irritability.

Depression may increase apathy. If depression is suspected, an SSRI should be tried. Sedative medication may increase apathy, thus avoiding unnecessary prescription or reduce dosage is recommended.

Anxiety

Anxiety as defined by the uncomfortable feeling of nervousness or worry about something that is happening or might happen in the future, is common in HD. Anxiety is linked to the other symptoms (motor and cognitive), as the patient is anxious because of the loss of essential functions, and correlated to family, social and economic issues, and to the burden of his pathology (and the one of his proxies). However, anxiety does not increase with disease progression. It is associated with depression, suicide, irritability, quality of life, pain, illness beliefs, and coping.

SSRI or SNRI are first line treatments of anxiety, especially when associated with depression. On-demand prescription of an anxiolytic might be beneficial, but caution is required because of the associated risk of worsening or causing falls. Neuroleptics[196-197] are valuable therapeutic alternatives in the treatment of anxiety when other treatments fail.

Obsessions

Obsessions are defined by recurrent and persistent thoughts, ideas or images that do not let the mind rest, causing anxiety. True obsessions, according to this definition, are not very common in patients with HD, but perseveration is very common, particularly in the middle and later stages.[186]

Perseveration may be defined as the repetition of a thought, behavior or emotion beyond the psychological context in which it arose, and in patients with HD these repetitive thoughts and

behaviors can persist for hours, months, or even years after the original trigger. Patients have little or no insight into the problem (in contrast to obsessional thoughts, which are distressing and recognized as abnormal); however, it has been shown that perseveration is the one behavioral symptom in HD which has a significant negative impact on the quality of life of family members and caregivers.[198]

Over the course of HD, symptoms may change and repetitive thoughts may replace obsessive–compulsive disorder. The distinction between obsessive–compulsive phenomena and perseverations is important for the care strategy, both requiring differential approaches. If pharmacological treatment is necessary for perseverative symptoms, an SSRI could be prescribed[199], in particular when symptoms are associated with anxiety. Olanzapine and risperidone[191, 196] are two valuable therapeutics for ideational perseverations, in particular when they are associated with irritability. True obsessive–compulsive phenomena are sensitive to psychological intervention, such as Cognitive Behavioral Therapy, in non-cognitively impaired patients. If pharmacological treatment is necessary for obsessive-compulsive phenomena, a SSRI should be prescribed as first-line treatment.[199]

Impulsivity

Impulsivity consists of acting without prior planning, which can lead to unpredictable behavior. When impulsivity is associated with depression or irritability, there is a significant increased risk of self-harm or suicide or aggressiveness. Impulsivity may be the result of cognitive impairments, which lead to an intense frustration toward patience, the patient being in the in capacity to wait or to deal cognitively with planning. Impulsivity may then be an adaptive response to language difficulties of patients who cannot explain what stresses them.

When impulsivity is associated with depression or personality disorders, there is a risk of auto- or hetero-aggressiveness, which justifies the prescription of a neuroleptic in combination with a SSRI. Long-term mood-stabilizer treatment may be introduced in the case of mood liability and impulsivity.

Sexual Disorders

Sexual disorders are very common in HD. Decreased libido is the most common symptom while hypersexuality or disinhibited behavior are rarer, but can cause significant problems in relationships. Repetitive hypersexual behaviors are often a result of perseveration.

Identifying the existence of sexual disorders and determining their triggers and their impact on relationships is important. Psychological support and/or referral to a specialist in psychosexual disorders might be useful. In the case of decreased libido, an iatrogenic cause should be investigated (e.g., the use of an SSRI) and reducing the dose or substituting the treatment responsible may be suggested.

In the case of erectile dysfunction, treatment for impotence may be suggested and seeking the opinion of an endocrinologist and/or a specialist in psycho-sexual disorders may be useful. In case of impotence, prescription of phophoesterase5inhibitors should be considered in the clinic when asked for by the patient and his sexual partner.

A behavioral and psychological approach is useful in the case of hypersexuality, by re-establishing appropriate standards of behavior in the patient's social setting. If hypersexuality involves social discomfort or violence, the proposed first-line treatment is a neuroleptic[200] and/or a SSRI.

If the treatment for hypersexuality with neuroleptics and/or SSRI is not successful, the addition of or substitution for an anti-androgen may be proposed[201-203] under the guidance of a specialist in sexual disorders or an endocrinologist. Where hypersexuality poses a risk to others, specific measures should immediately be put in place (e.g., referral to a psychiatrist).

Hallucinations

Hallucinations are defined as a perception without an object, at which the subject adheres to and reacts as if the perception came from outside. Delusions are false beliefs based on incorrect inferences about external reality, the cultural and social context to which the patient belongs.

The use by the patient of psychotropic agents should be searched for and interrupted in case of hallucinations and delusions. Second generation neuroleptics are the first line treatment for hallucinations and delusions.[190, 191, 196, 204-216]

Clozapine should be proposed as the first-line treatment in the case of akinetic forms of HD with debilitating Parkinsonian symptoms. Perseverative ideation can sometimes mimic psychotic symptoms, and in such circumstances the patient may benefit from treatment with serotoninergic antidepressants in combination with an atypical neuroleptic. Psychiatric intervention and support are particularly useful in the case of psychotic disorders occurring in

HD, for treatment adjustments. If pharmacological treatments fail, the option of ECT can be discussed with psychiatrists.[181, 183, 217]

In case of agitation, priority should be given to identifying environmental or somatic triggers (bladder distension, fecal impaction, pain, etc.) in order to treat the underlying cause, especially in the advanced stages of the disease when communication difficulties exist. When agitation is associated with an anxiety disorder, a benzodiazepine should be prescribed as needed to reduce the risk of dependence and falls(Professional agreement). Some benzodiazepines (e.g., midazolam) may be useful in emergency situations. Long-term treatment with benzodiazepines should be avoided as much as possible but remains necessary in some patients. In the case of extreme agitation, and if there are associated behavioral and personality disorders, it is advised to prescribe a neuroleptic.[192, 200, 201, 212, 218, 219]

Other Disorders

Other symptoms than motor, cognitive and psychiatric disorders are often present. Among those, weight loss, dysphagia, and sleep disturbance are not infrequently the most prominent symptoms. As they may cause discomfort, they should be looked for in order to limit them when present.

Sleep Disorders

Sleep disorders are common in HD. Around two-thirds of HD patients' suffer from sleep disorders, with diverse causes such as depression, anxiety, intrinsic alteration in the circadian sleep-wake rhythm, and involuntary movements during sleep inducing awakenings.[220, 221] They may present as difficulties in falling asleep and/or early awakenings in the middle of the night followed by insomnia. They may be associated with aimless wandering, and lead to difficulties in coping by the proxies. However, disturbances of diurnal rhythm (day-night reversal, etc.) are probably more common than simple insomnia in HD patients.

Potential underlying cause of sleep-related difficulties (e.g., depressive syndrome, anxiety, and severe involuntary movements) should be investigated. Simple lifestyle and dietary strategies (e.g., avoiding long nap, having no stimulants after 4 pm) are the first-line treatment of insomnia. When lifestyle strategies are in effective to treat insomnia, prescribing a hypnotic may be suggested for a short duration to avoid the risk of drug dependence.

Some agents may be proposed in place of a hypnotic and for a long duration (e.g., mianserin, mirtazapine, and antihistaminic drugs) as they have a reduced tendency for causing dependency. Melatonin may be suggested in case of sleep phase inversion. A neuroleptic should be prescribed in the evening when sleep disorders are associated with behavioral disorders or chorea.

Urinary Incontinence

Urinary incontinence may either be multifunctional or linked to a deterioration of the frontal lobe control centers, causing an overactive bladder with urge incontinence and/or unannounced urination.[222] Where there is urinary incontinence, a precipitating factor should always be investigated (urinary infection, prostate disease). It is useful to investigate the presence of diurnal unexpected complete urination (complete and sudden bladder emptying, without urge) for which carbamazepine may be of benefit.[222]

In the case of an overactive bladder with leakage and urge incontinence, therapy with selective antimuscarinic may be tried, whilst watching out for the appearance of potential side effects, in particular confusional state. If, after few weeks, the incontinence therapy has not been effective, it should be stopped. If simple therapeutic measures have failed, it is advised to undergo urodynamic testing to help guide the choice of drug therapy and to consult a urologist if necessary. In all cases, it is recommended to implement simple lifestyle strategies: urination before every outing and at regular times.

Pain

Pain assessment is sometimes difficult because of communication disorders. Moreover, because of communication's disorders and a tendency for these patients not to complain, pain is often related to non-verbal language and behavioral disorders such as irritability and restfulness. Behavioral change or worsening of involuntary movements should trigger the search for an underlying source of discomfort, and in particular pain.

Dental Pain

Patients suffer from poor oral health for a variety of reasons, including impaired motor ability(e.g., difficulties brushing teeth) or reduced motivation to maintain oral health, the use of drugs affecting salivary secretion and frequent dental trauma due to falls and injuries, bruxism.

Multidisciplinary teamwork, especially with dietitians to avoid highly cariogenic foods, is recommended.[223, 224] Verbal and written instructions on how to provide good oral hygiene at home should be given to patients and care givers.[224, 225] Dental care including descaling by a dentist or dental hygienist should be carried out at least once a year but should be more frequent in the later stages of the disease.

At later stages of the disease, treatment options should be discussed carefully and in advance. Treatment intervention, especially in late stage disease may require conscious sedation (midazolam, Diazepam) or general anesthesia in a hospital setting.[225-227]

In view of the frequency of digestive disorders in HD (e.g., constipation, diarrhea, and vomiting) and their impact on the quality of life of patients, routine assessment for these symptoms is recommended in order to ensure their management.

Their diagnostic workup should be conducted by the relevant specialists (general and digestive examination, biological and radiological tests, scan, fibroscopy, colonoscopy, etc.). Fecal impaction should be routinely investigated where there is constipation/ diarrhea ("false" diarrhea) and/or vomiting. Vomiting is sometimes intractable. If no specific etiology is identified, the following should be considered: staggering meals, reviewing the patients' posture during and after the meal, and possibly reducing antichoreic agents, in particular neuroleptics.

Excessive Perspiration

Excessive perspiration can occur at all stages of HD. It can be associated with other autonomic disorders and reflects discomfort or emotional burst when sudden.

In the case of excessive perspiration, care must be taken to ensure patients are well-hydrated, monitored and that their fluid and electrolyte balance is adjusted. Thyroid function and the possibility of infection should be assessed in case of excessive perspiration.

Weight Loss

Weight loss is often present in HD, sometimes prior to the appearance of other symptoms. It might occur despite normal, or even high calorie intake, due to a significant energy expenditure in HD patients. It can also be caused by swallowing disorders, depressive syndrome with reduced appetite or gastrointestinal disturbance and gut abnormalities due to enteric neuron dysfunction.[228]

Good nutritional care is a fundamental element of the management of HD.[229, 230] Early assessment by a dietitian or nutritionist, and regular timely reviews of nutritional needs are recommended. Factors such as swallowing ability, cognitive changes, behavior, mood, and general functional ability should be considered to determine possible other causes of weight loss.[132, 230-233]

A multidisciplinary approach is recommended and may include a Speech Language Therapist and an Occupational Therapist to assist with swallowing, positioning and feeding aids. Screening tools for malnutrition [e.g., malnutrition Universal Screening Tool (MUST)] are recommended.

A high Body Mass Index (BMI) within normal values should be maintained if possible and medical and/or social intervention is recommended when unintended weight loss is higher than 10% within last 3–6 months or when BMI is <20 kg/m2 and unintentional weight loss of 5% is observed within last 3–6 months. When weight loss is observed, high-calorie and high protein food supplements should be prescribed under instruction and monitored by a dietician/nutritionist.[234, 235]

A Mediterranean diet may improve Quality of Life and nutritional composition.[236]

In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss, whilst treatments inducing weight loss should be avoided (these effects can vary from one patient to another).[237]

Advanced care planning is essential and alternative feeding methods (PEG, see swallowing disorders) should be anticipated and discussed with relatives and patients still able to understand the benefits and risks of the intervention.

Hypersalivation

Hypersalivation can be troublesome in HD patients when associated with a salivary incontinence (caused by poor oral occlusion and or fault swallowing).

In the absence of a specific treatment for HD, drugs used in other chronic diseases may be considered to reduce salivary secretion: scopolamine given percutaneously, atropine given orally or other drugs that have an anticholinergic effect (amitriptyline), whilst watching out

for iatrogenic risks, in particular confusional state, constipation, ocular hypertension and urinary retention.

Injections of botulinum toxin into the salivary glands may be considered in a specialized setting if oral or oral mucosa treatment options have not induced benefit or were not well-tolerated.

Reduced Lung Function and Respiratory Muscle Strength

Reduced lung function and respiratory muscle strength are not only associated with end stage disease but occur much earlier, with evidence of some upper airway changes in pre-symptomatic individuals and reduction of cough effectiveness, reduced lung volume, and impaired respiratory strength by mid-disease. Along with changes in posture reduced exercise capacity, these impairments negatively impact respiratory function, leaving patients vulnerable to respiratory infections.

Home-based respiratory muscle training program appeared to improve pulmonary function in manifest HD patients but had only a small effect on swallowing function, dyspnea, and exercise capacity.[238]

PHARMACOLOGY OF MAJAR DRUGS USED IN HUNTINGTON'S DISEASE

TETRABENZINE

Indication

Treatment of hyperkinetic movement disorders like chorea in Huntington's disease, hemiballismus, senile chorea, Tourette syndrome and other tic disorders, and tardive dyskinesia

Associated Conditions

- Gilles de la Tourette's Syndrome
- Hemiballismus
- Huntington's Disease (HD)
- Tardive Dyskinesia (TD)
- Senile chorea

Pharmacodynamics

Prolongation of the QTc interval has been observed at doses of 50 mg. In rats, it has been observed that tetrabenazine or its metabolites bind to melanin-containing tissues such as the

eyes and skin. After a single oral dose of radiolabeled tetrabenazine, radioactivity was still detected in eye and fur at 21 days post dosing.

Mechanism of action

Tetrabenazine is a reversible human vesicular monoamine transporter type 2 inhibitor (Ki = 100 nM). It acts within the basal ganglia and promotes depletion of monoamine neurotransmitters serotonin, norepinephrine, and dopamine from stores. It also decreases uptake into synaptic vesicles. Dopamine is required for fine motor movement, so the inhibition of its transmission is efficacious for hyperkinetic movement. Tetrabenazine exhibits weak in vitro binding affinity at the dopamine D2 receptor (Ki = 2100 nM).

Table 6: Mechanism of action of Tetrabenzine.

Target	Actions	Organism
Synaptic vesicular amine transporter	inhibitor	Humans
Dopamine D2 receptor	inhibitor	Humans

Absorption

Following oral administration of tetrabenazine, the extent of absorption is at least 75%. After single oral doses ranging from 12.5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection because of the rapid and extensive hepatic metabolism of tetrabenazine. Food does not affect the absorption of tetrabenazine. Cmax, oral = 4.8 ng/mL in HD or tardive dyskinesia patients;

Tmax, oral = 69 min in HD or tardive dyskinesia patients

Volume of distribution

Steady State, IV, in HD or tardive dyskinesia patients: 385L. Tetrabenazine is rapidly distributed to the brain following IV injection. The site with the highest binding is the striatum, while the lowest binding was observed in the cortex.

Protein binding

Tetrabenazine = 82 - 88%; α-HTBZ = 60 - 68%; β-HTBZ = 59 - 63%.

Metabolism

Tetrabenazine is hepatically metabolized. Carbonyl reductase in the liver is responsible for the formation of two major active metabolites: α-dihydrotetrabenazine (α-HTBZ) and β-dihydrotetrabenazine (β-HTBZ).

α-HTBZ is further metabolized into 9-desmethyl-α-DHTBZ, a minor metabolite by CYP2D6 and with some contribution of CYP1A2. β-HTBZ is metabolized to another major circulating metabolite, 9-desmethyl-β-DHTBZ, by CYP2D6. The Tmax of this metabolite is 2 hours post-administration of tetrabenazine.

- **Tetrabenazine** - alpha-dihydrotetrabenazine

Route of elimination

After oral administration, tetrabenazine is extensively hepatically metabolized, and the metabolites are primarily renally eliminated (75%). Tetrabenazine is also cleared fecally (7% to 16%). Unchanged tetrabenazine has not been found in human urine. Urinary excretion of α-HTBZ or β-HTBZ (the major metabolites) accounted for less than 10% of the administered dose.

Half life

α-HTBZ = 7 hours; β-HTBZ = 5 hours; 9-desmethyl-β-DHTBZ = 12 hours.

Clearance

IV, 1.67 L/min in HD or tardive dyskinesia patients.

Toxicity

Dose-limiting adverse effects are sedation, parkinsonism, akathsia, and depression. LD50 oral, mouse: 550 mg/kg.[239-245]

CITALOPRAM

Indication

For the treatment of depression, as indicated by the FDA label. Off-label indications include but are not limited to: treatment of sexual dysfunction, post-stroke behavioural changes, ethanol abuse, obsessive-compulsive disorder (OCD) in children, and diabetic neuropathy.

Associated Conditions

- Anorexia Nervosa (AN)
- Bulimia Nervosa
- Depression

Pharmacodynamics

Citalopram belongs to a class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs). It has been found to relieve or manage symptoms of depression, anxiety, eating disorders and obsessive-compulsive disorder among other mood disorders. The antidepressant, anti-anxiety, and other actions of citalopram are linked to its inhibition of CNS central uptake of serotonin.

Serotonergic abnormalities have been reported in patients with mood disorders. Behavioral and neuropsychological of effects of serotonin include the regulation of mood, perception, reward, anger, aggression, appetite, memory, sexuality, and attention, as examples. The onset of action for depression is approximately 1 to 4 weeks. The complete response may take 8-12 weeks after initiation of citalopram.[246]

In vitro studies demonstrate that citalopram is a strong and selective inhibitor of neuronal serotonin reuptake and has weak effects on norepinephrine and dopamine central reuptake. The chronic administration of citalopram has been shown to down regulate central norepinephrine receptors, similar to other drugs effective in the treatment of major depressive disorder. Citalopram does not inhibit monoamine oxidase.[247]

Mechanism of action

The mechanism of action of citalopram results from its inhibition of CNS neuronal reuptake of serotonin (5-HT). The molecular target for citalopram is the serotonin transporter (solute carrier family 6 member 4, SLC6A4), inhibiting its serotonin reuptake in the synaptic cleft.[248]

Citalopram binds with significantly less affinity to histamine, acetylcholine, and norepinephrine receptors than tricyclic antidepressant drugs. This drug has no or neglible affinity for 5-HT1A, 5-HT2A, dopamine D1 and D2, α1-, α2-, and β- adrenergic, histamine H1, gamma-aminobutyric acid (GABA), muscarinic, cholinergic, and benzodiazepine receptors.

Antagonism of muscarinic, histaminergic, and adrenergic receptors is thought to be associated with several anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs.

Table 7: Mechanism of action Citalopram.

TARGET	ACTIONS	ORGANISM
Sodium-dependent serotonin transporter	inhibitor	Humans
Histamine H1 receptor	binder	Humans

Absorption

Rapidly and well absorbed from the GI tract. Peak plasma concentrations occur within 4 hours of a single orally administered dose. Bioavailability is 80% following oral administration. Food does not affect absorption.

Volume of distribution

12 L/kg

Citalopram is highly lipophilic and likely widely distributed throughout the body, including the blood-brain-barrier. However, its metabolite, *dimethyl citalopram* does not penetrate the blood-brain-barrier well.

Protein binding

Citalopram, dimethyl citalopram, and didemethyl citalopram are 80% bound to plasma proteins.

Metabolism

Citalopram is metabolized mainly in the liver via *N*-demethylation to its main metabolite, *dimethyl citalopram* by CYP2C19 and CYP3A4. Other metabolites include *didemethyl citalopram* via CYP2D6 metabolism, and *citalopram N-oxide* via monoamine oxidase enzymes and aldehyde oxidase. It is a deaminated propionic acid derivative.[249]

After a single dose of citalopram, peak blood concentrations occur at approximately 4 hours. This drug in is found mainly unchanged in the plasma as citalopram. Cytochrome P450 (CYP) 3A4 and 2C19 isozymes appear to be heavily involved in producing *demethylcitalopram*. Demethylcitalopram appears to be further *N*-demethylated by CYP2D6 to didemethylcitalopram. Citalopram metabolites exert little pharmacologic activity in comparison to the parent drug and are not likely to contribute to the clinical effect of citalopram.[250]

- Citalopram- demethylcitalopram
- Citalopra-N-Desmethylcitalopram

- Citalopram-Citalopram-N-oxide and inactive deaminated propionic acid derivative
- Citalopram-didemethylcitalopram

Route of elimination

12-23% of an oral dose of citalopram is found unchanged in the urine, while 10% of the dose is found in the faeces.

Half life

About 35 hours.

Clearance

The systemic clearance of citalopram is 330 mL/min, with approximately 20% renal clearance.

Toxicity

Oral (Human) LD: 56 mg/kg Intraperitoneal (Mouse) LD50: 179 mg/kg

Acute toxicity

Symptoms of toxicity include dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. Rarely, symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and extremely rare cases of cardiac torsade de pointes) may occur. Acute renal failure has been a rare occurrence.[250]

In cases of overdose, establish and maintain the airway to ensure adequate ventilation and oxygen delivery. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are advised, in addition to supportive care. With the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Pregnancy

This drug is categorized as pregnancy category C. In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, which includes teratogenic effects when given at doses higher than human therapeutic doses. There

are no sufficient and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only in cases where the potential benefit justifies the possible risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to celexa and other SSRIs or SNRIs, late in the third trimester, have undergone complications requiring prolonged hospitalization, respiratory support, and parenteral feeding. Complications such as these can arise immediately upon delivery.

Nursing Mothers

Citalopram is excreted in human breast milk. There have been two reports of infants demonstrating high levels of somnolence, reduced feeding, and weight loss associated with breastfeeding from a mother taking citalopram. In one specific case, the infant was reported to recover completely after the discontinuation of citalopram. In the second case, no follow-up information was available for assessment. The decision whether to continue or discontinue either nursing or celexa should consider the risks of citalopram exposure for the infant versus the benefits of celexa treatment for the mother.

RISPERIDONE

Indication

Risperidone is indicated for the treatment of schizophrenia, acute manic or mixed episodes associated with Bipolar I Disorder, and irritability associated with autistic disorder.

Risperidone is also used off-label for a number of conditions including as an adjunct to antidepressants in treatment-resistant depression.

Associated Conditions

- Acute Mania
- Agitation
- Delusional Parasitosis
- Gilles de la Tourette's Syndrome
- Irritability
- Mixed manic depressive episode
- Post Traumatic Stress Disorder (PTSD)
- Psychosis
- Schizophrenia

- Treatment Resistant Major Depressive Disorder
- Severe Dementia Alzheimer's type

Pharmacodynamics

The primary action of risperidone is to decrease dopaminergic and serotonergic pathway activity in the brain, therefore decreasing symptoms of schizophrenia and mood disorders.[251-252]

Risperidone has high affinity binding to serotonergic 5-HT2A receptors versus dopaminergic D2 receptors in the brain.[251, 253] Risperidone binds the D2 receptors with lower affinity than the traditional, first generation antipsychotic drugs, which bind with very high affinity. A reduction in extrapyramidal symptoms in Risperidone use is attributed to its moderate affinity for dopaminergic D2 receptors.[254, 255]

Mechanism of action

Though its mechanism of action is not fully understood at this time, current focus is on the ability of risperidone to inhibit the D_2 dopaminergic receptors and 5-HT2A serotonergic receptors in the brain. Schizophrenia is thought to be caused by an excess of dopaminergic D2 and serotonergic 5-HT2A activity, resulting in over activity of central mesolimbic pathways and mesocortical pathways, respectively.[251, 254, 256]

D_2 dopaminergic receptors are transiently inhibited by risperidone, reducing dopaminergic neurotransmission, therefore decreasing positive symptoms of schizophrenia, such as delusions and hallucinations. Risperidone binds transiently and with loose affinity to the dopaminergic D_2 receptor, with an ideal receptor occupancy of 60-70% for optimal effect.[255,257] Rapid dissociation of risperidone from the D_2 receptors contributes to decreased risk of extrapyramidal symptoms (EPS), which occur with permanent and high occupancy blockade of D_2 dopaminergic receptors.[255, 258] Low affinity binding and rapid dissociation from the D_2 receptor distinguish risperidone from the traditional antipsychotic drugs. A higher occupancy rate of D2 receptors is said to increase the risk of extrapyramidal symptoms and is therefore to be avoided.[255, 258,]

Increased serotonergic neocortical activity in schizophrenia results in negative symptoms, such as depression and decreased motivation.[260] The high affinity binding of risperidone to 5-HT2A receptors leads to a decrease in serotonergic activity. In addition, 5-HT2A receptor

blockade results in decreased risk of extrapyramidal symptoms, likely by increasing dopamine release from the frontal cortex, and not the nigrostriatal tract. Dopamine level is therefore not completely inhibited.[254, 255] Through the above mechanisms, both serotonergic and D_2 blockade by risperidone are thought to synergistically work to decrease the risk of extrapyramidal symptoms.

Risperidone has also been said to be an antagonist of alpha-1 (α1) alpha-2 (α2) receptors, and histamine (H1) receptors.[L1212] Blockade of these receptors is thought to improve symptoms of schizophrenia, however the exact mechanism of action on these receptors is not fully understood at this time.[260]

Table 8: Mechanism of action of Resperidone.

TARGET	ACTIONS	ORGANISM
5-hydroxytryptamine receptor 2A	antagonist	Humans
Dopamine D2 receptor	antagonist	Humans
Alpha-1A adrenergic receptor	antagonist	Humans
Dopamine D3 receptor	antagonist	Humans
Dopamine D4 receptor	antagonist	Humans
Alpha-1B adrenergic receptor	antagonist	Humans
5-hydroxytryptamine receptor 1D	antagonist	Humans
Histamine H1 receptor	antagonist	Humans
Alpha-2A adrenergic receptor	antagonist	Humans
Alpha-2B adrenergic receptor	antagonist agonist	Humans
Alpha-2C adrenergic receptor	agonist	Humans
5-hydroxytryptamine receptor 2C	antagonist	Humans
5-hydroxytryptamine receptor 1A	antagonist	Humans
Dopamine D1 receptor	antagonist	Humans
5-hydroxytryptamine receptor 7	Not Available	Humans

Absorption

Well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Volume of distribution

1 to 2 L/kg

Protein binding

Risperidone, ~88% bound in human plasma; 9-hydroxyrisperidone, ~77% bound in human plasma.[261]

Metabolism

Extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyrisperidone, which has approximately the same receptor binding affinity as risperidone.[258, 261]

Hydroxylation is dependent on debrisoquine 4-hydroxylase and metabolism is sensitive to genetic polymorphisms in debrisoquine 4-hydroxylase.[261] Risperidone also undergoes N-dealkylation to a lesser extent.[255, 261]

- **Risperidone**- 9-hydroxyrisperidone

Route of elimination

Risperidone is extensively metabolized in the liver. In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives are prolonged compared to young healthy subjects.[261]

Half life

3 hours in extensive metabolizers Up to 20 hours in poor metabolizers[261]

Clearance

Risperidone is cleared by the kidneys. Clearance is decreased in the elderly and those with renal creatinine clearance of 15 mL/min to 59 mL/min, which decreases clearance by 60%.

Toxicity

Symptoms of overdose include lethargy, dystonia/spasm, tachycardia, bradycardia, and seizures. LD_{50}=57.7 mg/kg (rat, oral) and 34 mg/kg (rat, intravenous).[254, 255, 258]

MIANSERIN

Indication

For the treatment of depression.

Pharmacodynamics

Mianserin is a tetracyclic antidepressant that has antihistaminic and hypnosedative, but almost no anticholinergic, effect. It is a weak inhibitor of norepinephrine reuptake and strongly stimulates the release of norepinephrine.

Interactions with serotonin receptors in the central nervous system have also been found. Its effect is usually noticeable after one to three weeks. Mianserin may cause drowsiness and hematological problems.

Mechanism of action

Mianserin's mechanism of therapeutic action is not well understood, although it apparently blocks alpha-adrenergic, histamine H1, and some types of serotonin receptors.

Table 9: Mechanism of action of Mianserin.

TARGET	ACTIONS	ORGANISM
U**Alpha-2A adrenergic receptor**	antagonist	Humans
U**5-hydroxytryptamine receptor 2A**	antagonist	Humans
U**5-hydroxytryptamine receptor 2C**	antagonist	Humans
U**Histamine H1 receptor**	antagonist	Humans
U**Sodium-dependent noradrenaline transporter**	inhibitor	Humans
U**Sodium-dependent serotonin transporter**	inhibitor	Humans
U**Histamine H4 receptor**	binder	Humans
U**5-hydroxytryptamine receptor 1A**	blocker	Humans
U**Alpha-2C adrenergic receptor**	antagonist	Humans
U**5-hydroxytryptamine receptor 2B**	binder	Humans
U**5-hydroxytryptamine receptor 1F**	binder	Humans
U**Alpha-2B adrenergic receptor**	antagonist	Humans
U**Dopamine D3 receptor**	binder	Humans
U**Kappa-type opioid receptor**	agonist	Humans
U**Sodium-dependent dopamine transporter**	binder	Humans
U**5-hydroxytryptamine receptor 7**	antagonist	Humans
U**Dopamine D2 receptor**	antagonist	Humans
U**5-hydroxytryptamine receptor 6**	binder	Humans
U**Alpha-1 adrenergic receptors**	antagonist	Humans
U**D(1) dopamine receptor**	binder	Humans

Absorption

Absorbed following oral administration.

Volume of distribution

Not Available

Protein binding

90%.

Metabolism

Hepatic.

- **Mianserin**- (R)-mianserin, N-Desmethyl
- **Mianserin**- (R)-mianserin, 8-hydroxy

Route of elimination

Not Available

Half life

10-17 hours

Clearance

Not Available

Toxicity

Oral rat LD_{50}: 780mg/kg[280-282]

PIRACETAM

Indication

Indicated in adult patients suffering from myoclonus of cortical origin, irrespective of etiology, and should be used in combination with other anti-myoclonic therapies.

PHARMACODYNAMICS

Piracetam is known to mediate various pharmacodynamic actions

Neuronal effects: Piracetam modulates the cholinergic, serotonergic, noradrenergic, and glutamatergic neurotransmission although the drug does not display high affinity to any of the associated receptors (Ki >10μM). Instead, piracetam increases the density of postsynaptic receptors and/or restore the function of these receptors through stabilizing the membrane fluidity.[283]

In the forebrain of aging mice, the density of NMDA receptors was increased by approximately 20% following 14 days of piracetam treatment. Based on the findings of various animal and human studies, the cognitive processes including learning, memory, attention and consciousness were enhanced from piracetam therapy without inducing sedation and psychostimulant effects. Piracetam mediate neuroprotective effects against hypoxia-induced damage, intoxication, and electroconvulsive therapy.[284]

In two studies involving alcohol-treated rats with evidences of withdrawal-related neuronal loss, piracetam was shown to reduce the extent of neuronal loss and increase the numbers of synapses in the hippocampus by up to 20% relative to alcohol-treated or alcohol-withdrawn rats.[283] This suggests that piracetam is capable in promoting neuroplasticity when recoverable neural circuits are present.[283] Although the mechanism of action is not fully understood, administration of piracetam prior to a convulsant stimulus reduces the seizure severity and enhances the anticonvulsant effectiveness of conventional antiepileptics such as carbamazepine and diazepam.[285]

Vascular effects:

Piracetam is shown to increase the deformability of erythrocytes, reduce platelet aggregation in a dose-dependent manner, reduce the adhesion of erythrocytes to vascular endothelium and capillary vasospasm. In healthy volunteers, piracetam mediated a direct stimulant effect on prostacycline synthesis and reduced the plasma levels of fibrinogen and von Willebrand's factors (VIII: C; VIII R: AG; VIII R: vW) by 30 to 40%.[285] Potentiated microcirculation is thought to arise from a combination of effects on erythrocytes, blood vessels and blood coagulation.[283]

Mechanism of action

Piracetam interacts with the polar heads in the phospholipids membrane and the resulting mobile drug-lipid complexes are thought to reorganize the lipids and influence membrane function and fluidity.[283]

Such interaction has been reported in a study that investigated the effects of neuronal outgrowth induced by beta amyloid peptides; while amyloid peptides cause lipid disorganization within the cell membranes leading to neuronal death, piracetam demonstrated to decrease the destabilizing effects of amyloid peptide.[286]

The authors suggest that piracetam induces a positive curvature of the membrane by occupying the polar groups in the phospholipids to counteract the negative curvature induced by amyloid peptides, which in turn would decrease the likelihood of membrane fusion.[283]

This mechanism of action is thought to improve membrane stability, allowing the membrane and trans membrane proteins to maintain and recover the three-dimensional structure or

folding for normal function such as membrane transport, chemical secretion, and receptor binding and stimulation.[283]

Through restored membrane fluidity, piracetam promotes restored neurotransmission such as glutamatergic and cholinergic systems, enhances neuroplasticity and mediates neuroprotective and anticonvulsant effects at the neuronal level. It is also demonstrated that piracetam also improves the fluidity of platelet membranes. At the vascular level, piracetam decreases adhesion of erythrocytes to cell wall and reduces vasospasm which in turn improves microcirculation including cerebral and renal blood flow.[283]

Absorption

Piracetam displays linear and time-dependent pharmacokinetic properties with low inter subject variability over a large range of doses. Piracetam is rapidly and extensively absorbed following oral administration with the peak plasma concentration is reached within 1 hour after dosing in fasted subjects.

Following a single oral dose of 3.2 g piracetam, the peak plasma concentration (Cmax) was 84 µg/mL. Intake of food may decrease the Cmax by 17% and increase the time to reach Cmax (Tmax) from 1 to 1.5 hours. Tmax in the cerebrospinal fluid is achieved approximately 5 hours post-administration.

The absolute bioavailability of piracetam oral formulations is close to 100% and the steady state plasma concentrations are achieved within 3 days of dosing.

Volume of distribution

V_d is approximately 0.6L/kg. Piracetam may cross the blood-brain barrier as it was measured in the cerebrospinal fluid following intravenous administration. Piracetam diffuses to all tissues except adipose tissues, crosses placental barrier and penetrates the membranes of isolated red blood cells.

Protein binding

Piracetam is not reported to be bound to plasma proteins.

Metabolism

As large proportion of total piracetam administered is excreted as unchanged drug, there is no known major metabolism of piracetam.

Route of elimination

Piracetam is predominantly excreted via renal elimination, where about 80-100% of the total dose is recovered in the urine. Approximately 90% of the dose of piracetam is excreted in the urine as unchanged drug.

Half life

The plasma half-life of piracetam is approximately 5 hours following oral or intravenous administration. The half-life in the cerebrospinal fluid was 8.5 hours.

Clearance

The apparent total body clearance is 80-90 mL/min.

Toxicity

The cases of overdose with piracetam are rare. The highest reported overdose with piracetam was oral intake of 75g which was associated with diarrhea and abdominal pain; the signs were most likely related to the extreme high dose of sorbitol contained in the used formulation.

In cases of acute, significant over dosage, stomach emptying by gastric lavage or induced emesis is recommended as there are no known antidotes for piracetam.

Management for an overdose will most likely be symptomatic treatment and may include hemodialysis, where the extraction efficacy of the dialyzer is 50 to 60% for the drug.

Oral LD50 in a mouse acute toxicity study was 2000 mg/kg.[286]

LEVETIRACETAM

Indication

Levetiracetam is indicated as an adjunctive therapy in the treatment of partial onset seizures in epileptic patients who are one month of age and older. Additionally, it is indicated as an adjunct in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy who are 12 years of age and older, and in primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy who are 6 years of age and older.

Levetiracetam is also available as an orally dissolvable tablet that is indicated as an adjunct in the treatment of partial onset seizures in patients with epilepsy who are 4 years of age and older and weigh more than 20kg.[287]

Associated Conditions

- Epilepsies
- Grand mal Generalized tonic-clonic seizure
- Partial-Onset Seizures
- Myoclonic seizures

Pharmacodynamics

Levetiracetam appears to prevent seizure activity via the selective inhibition of hypersynchronized epileptic form burst firing without affecting normal neuronal transmission, though the exact mechanism through which this occurs is unclear. The therapeutic index of levetiracetam is wide, making it relatively unique amongst other anti-epileptic medications.

Anti-epileptic drugs, including levetiracetam, may increase the risk of suicidal ideation or behavior - patients taking levetiracetam should be monitored for the emergence or worsening of depressive symptoms, suicidal ideation, and behavioural abnormalities.[288]

Mechanism of action

The exact mechanism through which levetiracetam exerts its anti-epileptic effects is unclear, but is thought to be unique amongst other anti-epileptic medications. Current knowledge suggests that levetiracetam's binding to synaptic vesicle protein 2A (SV2A) is a key driver of its action. SV2A is a membrane-bound protein that is found on synaptic vesicles and is ubiquitous throughout the CNS - it appears to play a role in vesicle exocytosis and in the modulation of synaptic transmission by increasing the available amount of secretory vesicles available for neurotransmission.[288] Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release,[289] but this action does not appear to affect normal neurotransmission. This has led to the suggestion that levetiracetam exclusively modulates the function of SV2A only under pathophysiological conditions.[290] Levetiracetam and related analogues showed a correlation between affinity for SV2A and anti-epileptic potency, further suggesting that action at this site contributes to the anti-epileptic activity of the drug.[288]

Levetiracetam has also been shown to indirectly affect GABAergic neurotransmission (despite having no direct effect on GABAergic or glutamatergic receptors) and modulate ionic currents.[288] Similarly, levetiracetam has been shown in vitro to inhibit N-type calcium

channels.[291] How, or even if, these actions are implicated in its anti-epileptic action have yet to be elucidated.

Table 10: Mechanism of action of Levetiracetam.

Target	Actions	Organism
Synaptic vesicle glycoprotein 2A	agonist	Humans
Voltage-dependent N-type calcium channel subunit alpha-1B	inhibitor	Humans

Absorption

Levetiracetam is rapidly and nearly completely absorbed following oral administration, with a reported absolute oral bioavailability of essentially 100%. T_{max} is approximately 1.3 hours after dosing, and C_{max} is 31 μg/mL following a single 1000mg dose and 43 μg/mL following repeated dosing. Co-administration of levetiracetam with food delays T_{max} by approximately 1.5 hours and decreases C_{max} by 20%.

Volume of distribution

The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg.

Protein binding

Levetiracetam and its metabolites are largely unbound to plasma proteins (<10%).

Metabolism

Levetiracetam is minimally metabolized within the body - the major metabolic pathway appears to be the enzymatic hydrolysis of its acetamide group which produces an inactive carboxylic acid metabolite, L057, which accounts for approximately 24% of the total administered dose. The specific enzyme(s) responsible for this reaction are unclear, but this pathway is known to be independent of hepatic CYP enzymes and has been proposed to be driven primarily by type B esterases in the blood and other tissues.[1] Two minor metabolites involving modifications to the pyrrolidone ring have been identified, one involving hydroxylation of the ring (constituting 1.6% of the total dose) and the other involving opening of the ring structure (constituting 0.9% of the total dose).

- **Levetiracetam**- Levetiracetam carboxylic acid metabolite (L057)

Route of elimination

Approximately 66% of the administered dose of levetiracetam is excreted in the urine as unchanged drug, while only 0.3% of the total dose is excreted via the feces. The primary

inactive metabolite of levetiracetam, L057, is also found in the urine as approximately 24% of the administered dose.

Half life

The plasma half-life of levetiracetam is 6-8 hours and is not affected by dose or repeat administration. Half-life is increased in the elderly (by about 40%) and those with renal impairment.

Clearance

The total plasma clearance of levetiracetam is 0.96 mL/min/kg, with renal clearance comprising 0.6 mL/min/kg. The primary inactive metabolite of levetiracetam, L057, has a renal clearance of 4 mL/min/kg. Given the relatively high proportion of drug undergoing renal clearance, overall clearance of levetiracetam is reduced in patients with renal impairment.

Toxicity

The oral TDLO of levetiracetam in humans is 10 mg/kg. Symptoms of levetiracetam overdose are consistent with its adverse effect profile and may include agitation, aggression, and somnolence, decreased level of consciousness, respiratory depression, or coma. There is no antidote for levetiracetam overdose; therefore management should involve general supportive measures and symptomatic treatment. Hemodialysis results in significant clearance of plasma levetiracetam (approximately 50% within 4 hours) and should be considered in cases of overdose as indicated by the patient's status.[292]

Future Perspectives

Huntington disease is the most widely studied genetic neurodegenerative disease that has available diagnostic and predictive genetic testing, with the possibility of gene-targeted therapy in the near future. Little is known about the normal cellular function of huntingtin or how its function is altered by an expansion f polyglutamine. Recent studies suggest that the polyglutamine expansion might enable mutant huntingtin to corrupt normal gene transcription[293] and to disrupt normal intracellular trafficking and transmitter release.[294, 295] But several issues remain with regard to how cellular dysfunction, including synaptic disturbances, can lead to neurodegeneration.

Molecular genetic approaches will be useful for dissecting the roles of various factors in HD. Improved understanding of such interactions will pave the way for targeting one or more of the aberrant protein–protein interactions in novel therapies.

Eventually, it might be feasible to develop drugs that alleviate the negative effect of polyglutamine expansions by interfering with specific pathways of gene expression or by altering undesirable protein–protein interactions.

This could allow intervention in the disease process very much upstream of the events that eventually lead to cell death. The idea that we might be able to inhibit events in the pathogenetic cascade early on raises the exiting possibility that ultimately the development of clinical symptoms might be completely prevented.[296]

CONCLUSION

HD is a devastating disease caused, in the vast majority of cases, by a genetic mutation that is readily identified independent of the onset of disease symptoms. It becomes increasingly clear that the cost of health is one of the major issues of public policy. In countries where there is a medical insurance system, the question of the choice of therapeutic care or medication and rehabilitation in the insured basket constitutes a central issue. The difficulty is even greater in rare diseases such as HD because the number of patients is too small to carry out double-blind placebo-controlled studies on large cohorts as required for the selection of health policies according to evidence-based medicine.

In parallel, thanks to specific international networks dedicated to HD (European Huntington's Disease Network (EHDN), HSG,andERN) experts' know-how has increased with a knowledge-learning culture over time. In this context, the French Ministry of Health has labeled Rare Diseases Reference Centers in 2004, imposing on them various duties, one of which is producing National Protocols for Diagnostics and Care (NPDC). EHDN, with more than 2,000 members in 50 countries, is concerned by the relevance of prescriptions, medical procedures, hospital stays, care pathways, and care arrangements.

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