Current views on pathophysiology and intervention in Huntington’s disease

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**Norsk sammendrag**

Huntingtons sykdom er en progressiv nevrodegenerativ sykdom som vanligvis medfører til døden 10-15 år etter sykdomsutbrudd. Årsaken til sykdommen er en repeterende ekspansjon av CAG i genet som koder for huntingtin proteinet, som i mutert form vil ha en overveiende toksisk effekt. De molekylære egenskapene til huntingtin proteinet er fremdeles ukjente. Diagnosen stilles basert på genetisk testing og kliniske undersøkelser av pasienten. Alderen for symptomdebut og sykdommens alvorlighetsgrad korrelerer med antallet CAG-repetisjoner. Huntingtons sykdom manifesterer seg ulikt hos forskjellige individer, med varierende grad av motoriske, kognitive og psykiske/psykiatriske symptomer. For øyeblikket er det ingen kurative behandlinger tilgjengelig og pasientene tilbys symptomatisk behandling, som vanligvis har mange bivirkninger. Hensikten med denne oppgaven er å gjennomgå tilnærmingen av behandling for Huntingtons sykdom pasienter, og den kliniske forskningen på patofysiologiske mekanismer. Denne litteraturgjennomgangen indikerer at selv om det foreløpig ikke finnes noen kurativ behandling er det likevel flere lovende forskningsområder, for eksempel medikamenter rettet mot DNA og RNA (inkludert antisense oligonukleotider), reduksjon av huntingtin proteinet (inkludert hemmere av proteinaggregater) og stimulering av autofagi maskineriet.
**English abstract**

Huntington’s disease is a progressive neurodegenerative disorder, which usually leads to death 10-15 years after the diagnosis. The cause of the disease is a CAG repeat expansion in the gene encoding the huntingtin protein, which will in its mutated form have a predominantly toxic effect. The molecular properties of the huntingtin protein are still unknown. The diagnosis is based on genetic testing and clinical examination of the patient. The age of onset of symptoms and severity of the disease correlates with the number of CAG-repeats. Huntington’s disease manifests differently in different individuals, with varying degrees of motor, cognitive, and mental/psychiatric symptoms. Currently, there are no curative treatments available and patients are offered symptomatic treatment, which usually have many side effects. The purpose of this thesis has been to review the current clinical approach to treatment of Huntington’s disease patients, and the clinical research into pathophysiological mechanisms and promising directions towards new experimental therapies for Huntington’s disease. This literature review indicates that while there currently is no curative therapies, there are several promising areas of research, e.g. therapies targeting DNA and RNA (including antisense oligonucleotides), huntingtin protein lowering strategies (including aggregation inhibitors) and autophagy enhancers.
1. Introduction

Huntington’s disease (HD) is one of the few neurodegenerative diseases with hereditary nature, and a history dating back several hundred years. But although the genetic mutation causative of HD was discovered in 1993, the pathophysiology of the disease is still largely unknown. There are several hypothesis and theories of how the disease progresses to give fatal neurodegeneration, but yet no definite answers. This lack of understanding affects the approaches to treatment and development of new therapies. As of today, there are no curative treatments available, and the symptomatic treatments administered only have vague responses, and even more side effects. The patient population affected by HD are few and scattered throughout the world. For these patients, and their families, HD is a devastating disease, which always ends fatally after many years of progressive decline. To possibly improve this situation, basic experimental research is needed to better understand the pathology and pathophysiology of the disease, and ultimately find a cure that can improve the otherwise somber prognosis for those affected.

On a positive side, since the 90s, the HD research field has been very productive and a literature search using the term ‘Huntington’s disease’ yields more than 20,000 original articles. Several reviews are available in different databases on HD, including different theories and hypothesis of both pathophysiology and therapy, but the scope of the amount of original articles makes it challenging to have a good overview. The aim of this project is to elucidate current views about the pathophysiology and the most promising effective treatments of HD based on available literature, both from online databases and information found in different textbooks. I will also give an overview and discuss different experimental treatment options from clinical trials that may deliver curative treatment in the future. While there are several reviews of the health care delivery practice in different countries, there are currently no reviews of how the health care delivery practice is organized in Norway. A secondary goal for the project is therefore to summarize the current clinical practice for management of HD patients at the University Hospital of Oslo, Norway.
2. Background

Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder of the brain associated with a trinucleotide expansion in the gene coding for the protein huntingtin (htt) on the short arm of chromosome 4 (Collaborative, 1993). The disease presents typically in mid-life with a progressive dementia and brief, abrupt involuntary movements described as dance-like by the observer, known as chorea (Cardoso, 2009), and is described to be hyperkinetic in nature, unlike the hypokinetic deficits seen in Parkinson’s disease (PD) (Roger A. Barker, Cicchetti, & Neal, 2012). The hyperkinetic movements reflects that the primary pathology in HD is the loss of the output neurons of the caudate putamen complex, which results in relative inhibition of the subthalamic nucleus and thus reduced inhibitory outflow from the globus pallidus and substantia nigra. This will lead to cortical motor areas being overactivated, generating an excess of movements, see Figure 1. Symptomatic treatment of the movement disorders is designed to reduce the level of dopaminergic stimulation within the basal ganglia. But there are no treatments for the cognitive decline, or curative treatment for the disease itself. (Roger A. Barker et al., 2012; Brodal, 2016)

![Diagram of the direct and indirect pathways in the basal ganglia.](image)

*Figure 1* Diagram of the direct and indirect pathways in the basal ganglia. Glu, glutamate; SNC, substantia nigra compacta; DA, dopamine; ACh, acetylcholine; Enk, enkephaline; GPe, globus pallidus externa; STN, subthalamic nucleus; GPi, globus pallidus interna; SNr, substantia nigra reticulate; VA, ventral anterior nucleus of the thalamus; VL, ventral lateral nucleus of the thalamus. Partly redrawn and based on Brodal (2016); Purves et al. (2018); Sontheimer (2015).
The history of Huntington’s disease, or Chorea Sancti Viti, officially starts in 1872 with George Huntington’s paper (Huntington, 1872). But the unofficial history starts long before, and goes all the way back to 1686 with Thomas Sydenham’s book *Schedula Monitoria de Novae Febris Ingressa* (Sydenham, 1688). Sydenham describes in detail the symptomatology of acute chorea, or chorea minor, and states that St. Vitus or St. John became in 1481 the saint of this disease when he interceded a dancing mania outbreak in Strasbourg. The association between chorea, St. Vitus and the earlier naming of the disease as Chorea Sancti Viti was due to individuals reporting afflicted with Chorea Sancti Viti were cured if they touched churches storing St. Vitus relics. The dance-like movement disturbances lead to the eponym St. Vitus’ dance also used to describe those afflicted. Individuals with Chorea Sancti Viti were kept isolated from other Strasbourg inhabitants in the Chapel of St. Vitus (Sydenham, 1688). In 1842 Dr. Charles Oscar Waters wrote a letter to the first edition of *The Practice of Medicine* where he described a condition known as ‘magrums’ (Dewey & Tupper, 2004). Waters concisely describes ‘magrums’ and the decline of motor and cognitive symptoms. He also described the hereditary nature of this condition, which we today believe was HD. Twelve years before George Huntington’s paper, a Norwegian doctor by the name of Johan Christian Lund, described a hereditary disease in the region Setesdalen, which he called ‘Rykkja’, meaning tremor (Lund, 1860). He unfortunately wrote his paper in Norwegian, and this did not capture the interest of the rest of the world. Lund’s observations as a general practitioner in Setesdalen rendered possible a full description of what we today call Huntington’s chorea or disease (Den Norske, 1996). What all these early scientists and doctors had in common was that they believed that there were no recovery, and when the disease started, it clung on until death. And as George Huntington said ‘It is one of the incurables’ (Huntington, 1872).

Before the discovery of the HD gene mutation in 1993, the prevalence of HD was described to be of 4-8/100,000 for the European population (Harper, 1992). Complete assertion of affected cases was not fully possible for big geographical areas, and the use of death records to determine prevalence was widely used, but unfortunately not ideal nor accurate (Conneally, 1984). The prevalence of HD varies with geographic location. In Western and European populations the prevalence is around 4-10/100,000 people, but more recent studies from the United Kingdom suggests it may be closer to 12.3/100,000 people (Baig, Strong, & Quarrell, 2016; Evans et al., 2013; M. Rawlins, 2010). The incidence in the Caucasian population is 0.11-0.8/100,000/year to 7.2/1,000,000/year (Pringsheim et al., 2012; Wexler et al., 2016). This makes HD one of the more common of the inherited neurologic diseases, with a
worldwide prevalence of 2.71/100,000 (Ghosh & Tabrizi, 2018; Pringsheim et al., 2012). HD occurs in all human populations worldwide, but is much more common in populations of European descent (Kay, Hayden, & Leavitt, 2017). Therefore it is thought that HD affected individuals migrated from North-Western Europe to other parts of the world. Even though migration is a major contributor of HD prevalence throughout the world, de novo mutations also make up a significant contribution to the prevalence of HD in the world. HD is uncommon in Africa with a prevalence between 0.06-7/100,000, depending on different regions of the African continent. Recent studies show that the prevalence is around 0.02-3.56/100,000, which may be due to weak ascertainment in communities with limited health care provision (M. D. Rawlins et al., 2016). China has a prevalence of 0.42/100,000 (Kay et al., 2017), while the Asian prevalence and incidence ranges from respectively 0.40/100,000 and 0.046-0.16/100,000/year (Pringsheim et al., 2012; M. D. Rawlins et al., 2016). United States and Canada has a prevalence of 5-13.7/100,000. An overall prevalence of about 5.63-12.1/100,000 is reported for Oceania. (Baig et al., 2016; Kay et al., 2017; M. D. Rawlins et al., 2016) HD has been shown to be less prevalent in Finland than the rest of Europe, at 2.12/100,000 people, which is speculated to be due to the relative genetic isolation. Given the high prevalence of HD in Northern European populations, it is surprising that HD occurs in only 1/100,000 in Iceland (Kay et al., 2017). In contradiction to the global population, the prevalence of HD is exceptionally high in some communities, especially those isolated from the rest of the population of the country. One example is a small community living near Lake Maracaibo in Venezuela, where the prevalence of HD is close to 700/100,000 people (Ghosh & Tabrizi, 2018). It is hypothesized that the high prevalence of HD in isolated communities is due to consanguinity. Genetic studies in individuals of this community led to the discovery of the genetic mutation causative of HD in 1993 (Collaborative, 1993). If the isolate HD community near Lake Maracaibo is excluded, the prevalence of HD in Venezuela is dramatically lower of only 0.5/100,000 (Kay et al., 2017).

With the identification and characterization of the HD gene on the short arm of the chromosome 4 in position 16.3 in 1993 (Collaborative, 1993; Nance, 2017), the genetic, epigenetic and molecular mechanisms of HD are still largely unknown. All humans have two allelic copies of the HD gene that encodes for the protein huntingtin (htt). The coding region of the gene encodes for the amino acid glutamine (CAG) at the 5’ end, called polyglutamine (polyQ) repeats, and they are usually amplified to a number ranging between 3 and 34, with most people having under 30 repeats. (Ghosh & Tabrizi, 2018; Nance, 2017; Sontheimer,
The role of these repeats are not well understood, but the presence of 40 or more repeats is considered a mutated gene with complete penetrance since essentially all carriers develop HD, assuming the resulting mutant huntingtin (mHTT) has become nonfunctional and toxic. Repeat numbers between 27 and 39 are considered mutable, they may or may not cause disease late in life. This is due to reduced penetrance since the gene does not necessarily translate to disease. There is an inverse correlation between the number of CAG repeats and age of onset of symptoms, as well as the rate of pathologic degeneration, which also correlate with the number of repeats (Abrams et al., 2010; Nance, 2017; Sontheimer, 2015). HD is inherited in an autosomal dominant fashion, which means that the phenotype of HD is completely dominant, and homozygotes for the disease allele do not differ clinically from heterozygotes. Therefore, HD follows a classical Mendelian inheritance pattern, which means that offsprings of an affected carrier have 50% chance of developing the disease if they inherit one allele (Abrams et al., 2010; Ghosh & Tabrizi, 2018; Nance, 2017; Sontheimer, 2015). An unique observation is that the disease can begin earlier and earlier in consecutive generations in some families. This is due to the inherent instability of the CAG repeat in gametes during meiosis, and can therefore lead to a change and expansion in the number of CAG repeats transmitted to the next generation. This phenomenon is known as genetic anticipation, and is most likely to happen from fathers to their offsprings. While on the other hand, affected mothers often transmit the abnormal gene in the same number of repeats, with a standard deviation of 3 repeats. (Abrams et al., 2010; Ghosh & Tabrizi, 2018; Nance, 2017; Sontheimer, 2015)

The presence of methyl groups on the DNA interferes with the binding of transcription factors and prevents transcription. Studies suggests that the DNA methylation machinery might be dysfunctional in HD with hypermethylation of DNA with consequently reduced expression levels of several genes. Impaired acetylation homeostasis and histone deacetylation has been shown to be dysfunctional in the pathogenesis of HD. Many microRNAs (miRNA) have been found downregulated in HD, contributing to gene dysregulation. The HTT gene locus produces a natural antisense transcript, called HTT-AS, which is alternatively splices and is highly expressed in some brain regions. It has been shown that this HTT-AS expression is reduced when there is an expanded CAG repeat present, and its regulatory effect on the htt transcript is revoked. (Bassi, Tripathi, Monziani, Di Leva, & Biagioli, 2017; Chung, Rudnicki, Yu, & Margolis, 2011)
So what is the function of the normal htt protein? Htt is a large water soluble protein that does not have any homology to other proteins. All cells throughout the body contains htt in their cell cytoplasm and it associates with the Golgi apparatus, endoplasmic reticulum, nucleus, neurites, and synapses and vesicles. The primary amino acid sequence contains a few known motifs that could provide information about huntingtins normal function. The polyQ region binds transcription factors, while a series of HEAT repeats, which are 40 amino acid long segments, mediate protein-protein interactions. There is a nuclear export signal, suggesting that htt may help transport molecules in and out of the nucleus. The htt protein also has several modulation sites where the htt activity can be altered through phosphorylation, ubiquitination, sumoylation and palmitoylation, which will induce reversible chemical changes and alter the biological functions of htt (Cattaneo, Zuccato, & Tartari, 2005). The htt protein itself participates to vesicle transport and recycling by interacting with several other proteins (i.e. HAP1, HAP40 and dynein) (Caviston & Holzbaur, 2009; Ravikumar, Imarisio, Sarkar, O'Kane, & Rubinsztein, 2008). As seen in the literature, the htt protein seems to have many functions, probably contributing to the difficulty of deciphering the pathophysiological mechanisms.

Several studies, including the COHORT (Dorsey et al., 2013) and PREDICT-HD study (Paulsen et al., 2014), have shown that symptoms of HD can begin many years before the onset of motor abnormalities. The TRACK-HD study included imaging and showed that changes in the brain can be detected 10-15 years before the onset (Tabrizi et al., 2013). The triad of symptoms characteristic for HD are divided into three groups: motor abnormalities, cognitive and behavioral impairment (Bates et al., 2015). The motor symptoms can be further classified into involuntary movements, such as chorea, and impairment of voluntary movements, for example incoordination, bradykinesia and rigidity. The involuntary movements, including chorea, are more prominent in adult-onset HD, while the impairment of movements are more common in juvenile-onset HD (Bates et al., 2015). One importance is to note that the impairment of the voluntary movements progresses more steadily throughout the disease progression and will therefore be a better prediction of functional disability than chorea and other involuntary movements (Rosenblatt et al., 2012; Rosenblatt et al., 2006). One motor symptom that is highly recommended to be studied is the presence of abnormalities of vertical saccades, with HD patients showing increased latency and slowing of saccades (Lasker & Zee, 1997; Willard & Lueck, 2014). Cognitive and behavioral impairment can occur several years before the onset of the motor symptoms (Stout et al.,
While the cognitive impairment is shown to progressively decline, the behavioral impairment is not described as progressive, but rather prominent than in the healthy population (Bates et al., 2015). Some of the cognitive problems HD patients encounter are problems of attention, mental flexibility, planning and emotion recognition, and cognitive slowing (Stout et al., 2012; Stout et al., 2011). There is evidence of problems with emotion recognition, which impairs the recognition of all negative emotions, particularly in the facial and vocal domain, including recognition of anger (Henley et al., 2012). The behavioral impairments include depressive symptoms, anxiety, irritability, delusional depression, and schizophrenia-like psychosis (Bates et al., 2015). Apathy is one of the few behavioral symptoms that is shown to be progressive (van Duijn et al., 2014).

The symptoms of HD greatly impacts the quality of life, and give rise to several complications associated with the disease. Gait and balance impairments are one important complication that both predicts nursing home placement and mortality. In manifest HD, several gait parameters are affected, including reduced velocity, reduced step and strides, increased amplitude and velocity of mediolateral sway of truncal movement, worsened balance with greater time spent in support and broader stance. Cadence is also significantly reduced in manifest HD (Vuong, Canning, Menant, & Loy, 2018). Patients with HD may have limited insight into motor, behavioral and cognitive deficits, and this loss of awareness (anosognosia) contributes to patients with HD under-reporting the presence or severity of involuntary movements, under-estimate cognitive impairment and deny behavioral changes (Sitek, Thompson, Craufurd, & Snowden, 2014). Autonomic dysfunction frequently accompanies HD, and patients report of significantly more gastrointestinal, urinary, sexual and cardiovascular problems. Studies have shown that cardiac autonomic control might become deregulated in HD, which can contribute to arrhythmias (Abildtrup & Shattock, 2013). Unintended weight loss complicates the course of HD and is present particularly in its final stages, contributing substantially to both morbidity and mortality. Many studies have demonstrated that HD patients are either underweight or tend to lose weight during the course of their illness, eventually becoming cachectic. Weight loss in HD is associated with an increased appetite, and undernutrition is common in HD patients. Conversely, a higher body weight at the time of diagnosis is associated with slower disease progression. (Aziz et al., 2008; Myers et al., 1991)

HD is diagnosed based on clinical evaluation, family history and genetic testing (Quaid, 2017). The diagnosis is primarily based on the unified HD rating scale (UHDRS) ("Unified
Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group, 1996) (See Supp.File 2). A UHDRS total motor score (TMS) of 15 or above is strongly supportive of the diagnosis (Bates et al., 2015). The diagnosis of HD can be further validated by imaging, such as structural MRI, CT or PET with radioactive labeling for htt protein. Imaging can be valuable, but is not necessary for the diagnosis of HD. There is however a set of potential biomarkers that can provide important information on drug effects, the traits and severity of the disease (Bates et al., 2015; Rodrigues, Byrne, & Wild, 2018). The differential diagnosis of HD is vast, including Huntington disease-like 2 syndrome (HDL2, also autosomal dominant), spinocerebellar ataxia, neuroacanthosis, benign hereditary chorea, and Sydenham’s chorea (Bates et al., 2015). Because juvenile HD does not have the same clinical presentation, it tends to be more difficult to diagnose, due to the presence of rigidity instead of chorea.

The disease progresses relentlessly, typically causing death 15-20 years after the initial diagnosis, most frequently from complications such as falls or aspiration. Motor incoordination causes frequent falls, while the failing coordination of facial and laryngeal muscles eventually makes speaking impossible and swallowing food a major challenge. This will impact eating and patients have great difficulty both eating and drinking, and begin to lose weight. Sufficient food intake will be even more challenging with the motor incoordinations including those of the facial and laryngeal muscles.(Sontheimer, 2015)

A study from Solberg et al. (Solberg, Filkukova, Frich, & Feragen, 2018) examined the age of death and the causes of death in individuals with HD in Norway. Mean age of death in individuals with HD was found to be 63.9 years (The Norwegian Cause of Death Registry, NCDR) and 61.7 years (The Center for Rare Disorders, CRD), compared to a mean of 76.9 years in the general population. No significant gender differences were found. In 73.5 % the underlying cause of death was HD, following by cardiovascular diseases, cancer and respiratory diseases. The most common immediate cause of death was respiratory diseases (44.2 %), with suicide following with 2.3 %. Other causes of death are choking, nutritional deficiencies, chronic skin ulcers and heart disease. Up to one-fifth of individuals with premanifest HD report history of suicidal ideation and one-of-14 report current suicidal ideation, compared to one-third and one-tenth of those with manifest HD report history and current of suicidal ideation. Both a history of past and current suicidal ideations were more frequent in manifest HD compared to premanifest HD. Throughout the progression of HD, a history of suicidal ideation and the presence of depressive symptoms were strongly
associated. However, while for the premanifest HD patients, socio-demographics and activities of daily living (ADL) appears to be more important. (Honrath et al., 2018)

There are currently no treatments available that can modify the disease progression, but symptom-modifying treatments are available and widely used. Symptomatic treatment of the behavioral and psychiatric deficiencies are mainly antipsychotic or antidepressive treatments. Unfortunately, the cognitive decline are difficult to treat. In the treatment of patients with HD, much emphasis is on sufficient nutrient intake and to prevent injury from falls and asphyxiation from poor control of laryngeal muscles. (Sontheimer, 2015)
3. Treatment of Huntington’s disease; the present and the future

The progressive nature of HD makes the development of curative therapies challenging. There are, as of today, no cure or disease-modifying therapies available. The clinical presentation and the progressive nature makes care for HD patients complex. There is a large necessity for multidisciplinary cooperation between neurologists, medical geneticists, psychiatrists, palliative care providers, specialized nurses and other health professionals offering services related to physical therapy, occupational therapy, speech and language therapy, nutrition, and social work (Mestre & Shannon, 2017). The multidisciplinary team can provide several options for the symptomatic treatment in HD, but the only two treatment options approved specifically for chorea HD is tetrabenazine and its derivative deutetrabenazine (Mestre & Sampaio, 2017). The symptomatic treatment of HD is categorized into three groups, interventions for the motor symptoms, the cognitive and the behavioral symptoms.

Tetrabenazine and deutetrabenazine are mainly used for the motor symptoms, and specifically chorea. The efficacy of deutetrabenazine was evaluated in two phase II clinical trials, FIRST HD and ARC-HD (Frank et al., 2016), showing that the drug is safe and well tolerated. Both clinical trials showed that effective control of chorea was achieved, maintained and improved during treatment (Bashir & Jankovic, 2018; Dean & Sung, 2018). Non-pharmacological management of the movement disorders are physical therapy and exercise, which seem safe and achievable for HD patients. It has been shown that exercise has beneficial effects on the cardiovascular and mitochondrial function, while beneficial effects on motor symptoms has not been demonstrated, but positive effects seems likely (Fritz et al., 2017; Mueller, Petersen, & Jung, 2019). Because our current knowledge of the non-pharmacological management are limited and based on small-scale studies the results can not be transferred to all HD patients, and there is a need for longer intervention studies (Mueller et al., 2019).

The medical treatment of the behavioral symptoms in HD is complex with limited evidence. Depression in HD is related to several factors, including the burden of having a genetic disease and the progressive decline that follows. The management of depression in HD is the same as for the general population. First line treatment, mainly used for mild depression, is supportive counseling, psychoeducation and different psychotherapeutic methods with a psychologist or psychiatrist. Second line treatment, used for moderate to severe depression and for patients resistant to non-pharmacological interventions, is the use of antidepressants. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are some of the antidepressants mostly used, but there is no consensus of
one drug being better. (Anderson et al., 2018; van Duijn, 2017) For anxiety it is advised that
general practice guidelines is followed, with SSRIs and SNRIs as first line pharmacological
treatment (Dale & van Duijn, 2015; van Duijn, 2017). There are no clinical evidence for the
treatment of irritability, but most often antipsychotic treatment are the first option, especially
if the irritability is acute or accompanied by impulsivity, aggression or hypersexuality (van
Duijn, 2017). When apathy occurs, and other causes, including depression or drug-related
causes are excluded, either counseling or pharmacological treatment with the antidepressant
Bupropion can be attempted (Anderson et al., 2018; Gelderblom et al., 2017; van Duijn,
2017). Treatment of psychosis in HD is as the same as for the general population, with
antipsychotic medication being first line treatment (Anderson et al., 2018; van Duijn, 2017).

The cognitive symptoms in HD implicate a frontostriatal dysfunction, including reduced
attention and executive functions (Lawrence et al., 1998). Studies with Atomoxetine, a
selective norepinephrine reuptake inhibitor used to treat attention deficit hyperactivity
disorder, has shown no significant improvement of the cognitive symptoms that accompanies
HD (Beglinger et al., 2009). As of today, there are no treatment that can stop, slow down or
reverse the cognitive symptoms in HD.

In addition to both non-pharmacological and pharmacological interventions, there are some
clinical trials and studies evaluating the benefits of surgical interventions in HD, including
stem cell transplantation and deep brain stimulation (DBS). The theory behind how DBS
works, especially in PD, has rendered theories of providing a means of treatment for the
motor symptoms in HD. But, several studies have shown that the beneficial effects of DBS in
HD is transient, and does only improve chorea, but not dystonia or bradykinesia (Adam &
Jankovic, 2008; Gonzalez et al., 2014). Experiments with stem cell transplantation for HD
patients has shown some improvement in the motor scale, tested by UHDRS ("Unified
Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group,"
1996). The transplantation did not lead to dramatic improvement of symptoms after 1 year,
but the treatment also has not shown any deleterious effects (Bachoud-Levi et al., 2000; R. A.
Barker et al., 2013).

Palliative care and HD-specific nursing homes focuses on the management of symptoms to
improve the quality of life for the patients and their families, and is most often initiated in
advanced stages of disease (Mestre & Shannon, 2017). The focus on implementation of
palliative care may delay admission to a nursing home, due to many palliative care programs
being based on community support (Mestre & Shannon, 2017). An integration of palliative
care and admission to a nursing home for HD patients would entail multidisciplinary team involvement, and even with weak evidence is recommended by clinicians (Mestre & Shannon, 2017).

As stated above, there are as of today only symptomatic treatment, and no curative therapies available. Several clinical studies have investigated diverse target molecules modifying the underlying pathogenesis, primarily based on biological measures of disease (Bates et al., 2015), with an increasing focus on investigation of premanifestation stages. Some of the future therapeutic approaches is shown in the Figure 2, and include therapies targeting DNA and RNA (Wild & Tabrizi, 2017), htt lowering strategies, immunotherapies (Denis, Laueroul, & Cicchetti, 2019), phosphodiesterase10A (PDE10A) inhibition (Cardinale & Fusco, 2018; Fusco & Paldino, 2017), neuroprotective steroids (Bansal & Singh, 2018), autophagy enhancers (Croce & Yamamoto, 2019; Martin, Ladha, Ehrnhoefer, & Hayden, 2015), and creatine therapy (Tabrizi et al., 2003, 2005). (Bates et al., 2015; Mestre & Shannon, 2017). With increasing understanding of how mHTT induce neuronal dysfunction and death, a multitude of therapeutic targets have been developed (Bates et al., 2015). One of the approaches is lowering the concentration of mHTT in the neurons to prevent its toxic effects. This can be done by designing selective oligonucleotides that bind DNA or RNA and target them for degradation (Wild & Tabrizi, 2017). One such selective oligonucleotide is the antisense oligonucleotide (ASO), which has shown promising results in phase II clinical trials (Tabrizi, Leavitt, et al., 2019).

Htt lowering strategies can be divided in DNA-targeting strategies, RNA-targeting approaches and lowering of mHTT. DNA targeting strategies use specific DNA binding and effector elements together. They either modulate gene transcription, or target htt DNA by direct modification, also called genome editing (Tabrizi, Ghosh, & Leavitt, 2019). Effector elements can be either nucleases (e.g. zinc-finger, transcription activator-like effector nucleases, Cas9), epigenetic modulators, or transcription factors (Tabrizi, Ghosh, et al., 2019). RNA-targeting approaches modulates the RNA post-transcriptionally and include RNA interference (RNAi) and ASOs (Tabrizi, Ghosh, et al., 2019), triggering cleavage, enhanced degradation or suppression of the translation of mHTT. Lowering of mHTT can also be based on the enhancement of the cellular clearance by increasing the several degradation systems. This includes the ubiquitin-proteasome system (UPS) and autophagy (Tabrizi, Ghosh, et al., 2019), where the UPS remove soluble and short-lived proteins, and larger aggregates are removed by autophagy. Studies of enhancement of the cells own degradation systems are still in the
preclinical stages (Harding & Tong, 2018; Tabrizi, Ghosh, et al., 2019; Tomoshige, Nomura, Ohgane, Hashimoto, & Ishikawa, 2018). Autophagy is another hot topic within HD research, due to several studies showing the important role of the lysosome-mediated degradation pathway macroautophagy (MA) in the clearance of the mHTT aggregates within the neurons (Croce & Yamamoto, 2019). MA is not the only exclusive autophagy pathway, it is only one of three autophagy pathways, but there are robust evidence that MA contributes largely to the degradation and elimination of mHTT aggregates (Croce & Yamamoto, 2019). A link between autophagy and HD clearly exists, with animal models studies showing that htt plays a significant role in autophagy (Croce & Yamamoto, 2019; Zheng et al., 2010).

Even with future therapeutic approaches looking promising, there is as of today no curative treatment for Huntington’s disease. One important task before implementing a treatment for HD is to understand the extensive effects of both normal htt protein and its mutated form mHTT. This demands comprehensive knowledge of the pathophysiology of Huntington’s disease.

**Figure 2 Current preclinical treatment targets under investigation for HD.** Several targets have been identified for the utilization as curative treatment for HD. Ac, acetyl group; ASO, antisense oligonucleotide; BDNF, brain-derived neurotrophic factor; CB2, cannabinoid receptor 2; EAA2, excitatory amino acid transporter 2; GM1, monosialotetrahexosylganglioside; HDAC4, histone deacetylase 4; INK, c-Jun N-terminal kinase (MAPK8, MAPK9 and MAPK10); KMO, kynurenine 3-monoxygenase; MAPK, mitogen-activated protein kinase; NMDA, N-methyl-d-aspartate; P, phosphate group; p38, mitogen-activated protein kinase (MAPK11, MAPK12, MAPK13 and MAPK14); PDE, phosphodiesterase; PPAR-γ, peroxisome proliferator-activated receptor-γ; RNAi, RNA interference; Su, sumoyl group; TrkB, tyrosine receptor kinase B. Figure adapted from Bates et al. (2015).
4. What is known about the pathophysiology?

Much is known about HD, but a complete understanding of the underlying pathophysiology has remained elusive despite considerable research investments. Our understanding of the disease mechanisms in HD expanded after the genetic causative of HD was discovered in 1993 by the worldwide collaboration The Huntington Disease Collaborative (Collaborative, 1993).

One of the hallmarks of HD is the progressive bilateral atrophy and neuronal loss of the caudate putamen complex. This is mainly caused by the GABAergic medium spiny projection neurons (MSNs), which is the main targets for striatal input and provides efferent output to the globus pallidus (Rub et al., 2016). These highly susceptible MSNs account for almost 95% of all neurons in the caudate putamen complex. Recent investigations have shown that the whole cerebral cortex undergoes atrophy, which could explain the cognitive and behavioral symptoms that accompanies HD (Rub et al., 2016). From an anatomical point of view, the loss of the GABAergic output MSNs in the caudate putamen complex will result in reduced inhibitory signals to the globus pallidus. These neurons comprise mainly the indirect pathway of the basal ganglia, while the direct pathway is not as strongly influenced. The globus pallidus externa sends normally inhibitory signals to the subthalamic nucleus, but in HD these inhibitory signals are increased, resulting in loss of excitatory signal to the globus pallidus interna and substantia nigra reticulata, which further will entail loss of inhibitory signal to the thalamus. The result of this pathway is thalamic nuclei increasing their excitatory signals to cortical motor areas, producing the hyperkinetic movements that is another hallmark of HD. See Figure 3.

The htt protein is expressed at varying levels throughout the body depending on the cell type, with a high density in neurons (Bates et al., 2015). I discussed the normal function of htt earlier, but at the same time, the specific biochemical function of the protein is still largely unknown (Bates et al., 2015). It has been shown in animal models that a germ-line deletion of htt causes embryonic lethality, and surprisingly, this lethality can be protected by the presence of mHTT (Sontheimer, 2015). Expression of htt under 50% during embryological development causes impaired neurogenesis and malformations of both the cortex and caudate putamen complex (Sontheimer, 2015). The biological function of htt in influencing the transcription and axonal transportation of brain-derived neurotrophic factor (BDNF) in neurons and the corticostriatal synapses (Bates et al., 2015; Sontheimer, 2015), resulting in reduced concentration of BDNF in HD (Zuccato & Cattaneo, 2007). But htt also interacts
with other proteins involved in the axonal transport in neurons, including the transportation of organelles through the axons (Sontheimer, 2015). At synapses, htt interacts with several proteins, and an inappropriate regulation of the interaction by the increasing concentration of mHTT contributes to receptor-mediated toxicity and a dysfunction in the communication between neurons (Bates et al., 2015; Sontheimer, 2015).

**Figure 3** Overview of the direct and indirect pathway disruption in the basal ganglia system during HD. Glu, glutamate; SNc, substantia nigra compacta; DA, dopamine; ACh, acetylcholine; Enk, enkephaline; GPe, globus pallidus externa; STN, subthalamic nucleus; GPi, globus pallidus interna; SNr, substantia nigra reticulate; VA, ventral anterior nucleus of the thalamus; VL, ventral lateral nucleus of the thalamus. Partly redrawn and based on (Brodal, 2016; Purves et al., 2018; Sontheimer, 2015).

It is thought that mHTT causes disease in two ways: deleterious effects of the mutated protein (negative gain of function), or aggregation into inclusion bodies (IB) with a loss of function of the protein (Sontheimer, 2015). It is the negative gain of function theory that is most prevalent, with researchers considering mHTT being toxic to the cells (Sontheimer, 2015), but
the loss of function resulting in aggregation of mHTT into IBs also contributes to the disease. The aggregation of mHTT into IBs in regional selective areas is considered one of the central hallmarks of HD, although their role in HD pathogenesis remains incompletely understood, with the selective loss of MSNs in the striatum to succumb to the IB aggregation first. There is however, a strong support for the notion that trafficking of misfolded proteins in IBs is the key to understanding the pathology of HD (Sontheimer, 2015). There are several theories to why MSNs selectively degenerate as part of the HD pathogenesis, but recent studies show that components of autophagy, the UPS, and chaperone systems are expressed or regulated differently in striatal neurons than in other brain regions. (Croce & Yamamoto, 2019; Margulis & Finkbeiner, 2014; Soares, Reis, Pinho, Duchen, & Oliveira, 2019)

One emerging model of HD pathogenesis proposes that the chronic production of misfolded mHTT overwhelms the chaperone machinery, diverting other misfolded clients to the proteasome and the autophagy pathways, ultimately leading to a global collapse of the proteostasis network. Multiple converging hypotheses also implicate ageing and its impact in the dysfunction of organelles as additional contributing factors to the collapse of proteostasis in HD. In particular, mitochondrial function is required to sustain the activity of ATP-dependent chaperones and proteolytic machinery. Recent studies elucidating mitochondria-endoplasmic reticulum interactions and uncovering a dedicated proteostasis machinery in mitochondria, suggest that mitochondria play a more active role in the maintenance of cellular processes than previously thought. (Soares et al., 2019)
5. Current situation in Norwegian hospital care

Ninety-five % of the patients seeking public medical help in Oslo have a positive family history of HD, where someone in their close family have experienced symptoms or have been diagnosed with HD. The department of medical genetics at Oslo University Hospital (OUH) have a presymptomatic genetic test program for individuals with known HD in their family who want to be tested. There is a need for a referral to the presymptomatic genetic test program, and the program is set up in accordance with international guidelines, and involves a preliminary interview, assessment by a psychologist or psychiatrist, a test interview, and a response interview. A physician, most often a medical geneticist, and a genetic counselor will be responsible for the information given and for conduction of these conversations. The psychological assessment is done to help the individual seeking presymptomatic genetic testing clarify the psychological stress a test entails, thus ensuring that the individual is well prepared to receive the answer. Once the presymptomatic genetic testing underlies a positive test, the individual, now the patient will receive the question of whether they want a referral to a neurologist. Most of the patients agree to the referral, and will seek the medical assistance of a neurologist, but some will decline the offer and seek medical assistance once the symptoms debut. The 5 % rest of the patients with HD do not have a positive family history that they know of. This could either be due to anticipation, subclinical chorea or an actual positive history of HD of which was unknown or the family member died before clinical symptoms.

Once at the neurologist’s office, the patients will undergo extensive clinical examination. A positive genetic test does not equals the diagnosis of HD, but rather the motoric phenotype, which is specific for HD. The diagnosis is as of today based on The Unified HD Rating Scale (UHDRS), including both motor, cognitive, behavioral and functional assessment. A positive clinical assessment will be followed by staging of the disease. In Norway, the staging of HD is not 5-phased, but 3-phased with an early phase, an intermediate phase and an advanced phase.

Every patient will receive the possibility to have a yearly check-up at the neurologist. Nevertheless, if there is a need for more extensive check-ups, or the patient himself/herself wants more frequent check-ups, this is offered. The patient will also receive multidisciplinary treatment from both physiotherapists, speech therapists, psychologist/psychiatrists and rehabilitation programs. To receive a diagnosis in Norway entails for not only help with medical assistance, but also with work and daily life situation. Patients will also receive help.
from the Norwegian Labour and Welfare Administration (NAV) during their lifetime with the
disease.

Treatment of HD in Norway is mainly focused to reduce the pain caused by the symptoms,
and pharmacological symptomatic treatment is often started when the symptoms are
becoming too inconvenient for the patient. The only approved pharmacological medication
for chorea and the motor symptoms in Norway consists of tetrabenazine and deutetrabenazine,
known as Tardiben. Tardiben is given as oral doses 1-3 times a day, with a maximal dose of
200 mg/day. Symptomatic treatment of depression, personality changes, aggression, and
irritability is mainly treated by atypical neuroleptics as olanzapine and risperidone, and
antidepressive SSRIs as Cipralex. The dystonia accompanying HD is primarily treated with
the spasmolytic Baclofen. Patients with juvenile HD struggle early with rigidity and can get
spastic paraparesis. This is usually combated with PD medication, such as levodopa. One side
effect of such treatment is worsening of the choreatic movements. Non-pharmacological
treatments such as deep brain stimulation (DBS) and stem cell transplantation are currently in
clinical trials, but have not been experimented with in Norway, due to its short time of effect
in patients with HD.

The progressive nature of HD will lead to patients being in need of nursing. These patients
will be admitted to a nursing home, and there are some nursing homes specifically designed
for HD patients. As the disease progresses these patients will need help for eating and all the
activities of daily living, such as brushing their teeth and so on. Because most patients will
suffer from risk of getting aspiration pneumonia, these patients will benefit from a
percutaneous endoscopic gastronomy (PEG), both for food and medication administration.
For terminally ill patients in Norway, the palliative care program is initiated, with the priority
of analgesia for the patients.
6. Discussion

In this thesis I have described the current views on pathophysiology and intervention in HD, as well as the current situation in Norwegian health care system in regards to HD patients. The scope of the current hypotheses on pathophysiology and future therapeutic approaches is beyond the scope of this thesis, but a general overview of the current information about HD is given. Since the identification of the gene causative of HD in 1993, research on HD has increased. Even though at present, only symptomatic treatment is available, researcher are seeking for disease-modifying treatments. There is a link between the pathology and pharmacology in HD, but this link is not fully understood.

Several theories exists regarding the pathogenesis of HD, all complementing each other. Some believe the answer to understanding why a CAG-expansion results in HD lies in the gene itself, because a faulty gene will not be transcribed to RNA, and no RNA means there will be no translation into protein (Sontheimer, 2015). Others hypothesize that it is the toxic effect of the aggregated protein that results in the death of MSNs in caudate putamen complex. While others again believe, there is an innate sensitivity of the MSNs, making them vulnerable to cellular changes, causing apoptosis and atrophy.

Since recent studies have shown a direct link between autophagy and HD, whether autophagy can be a therapeutic approach has been extensively studied (Croce & Yamamoto, 2019). No evident deficits has been reported in MA in HD patients, suggesting that there is a possibility for selective activation of the MA system, which could be a possible therapeutic approach (Croce & Yamamoto, 2019; Hodges et al., 2006; Kuhn, Thu, Waldvogel, Faull, & Luthi-Carter, 2011). Autophagy is considered a link between pathogenesis of HD with aggregated mHTT proteins and a means of future therapeutic effects for disease modification of HD (Croce & Yamamoto, 2019). The link between autophagy and pathogenesis of HD is mainly explained by the significance of htt in vesicle trafficking, but in vivo studies in humans are needed to conclude whether MA could be the cure (Croce & Yamamoto, 2019).

Future clinical trials aimed at modifying the pathogenesis will increasingly rely on biological measures of disease activity (Bates et al., 2015), and expanded investigation of intervention in the premanifestation stages of HD are today a focus, and will be even more in the future. There is a huge effort in finding a cure or disease modifying treatment, but one important area is the delivery of the pharmacologic agent. All agents that will in the future be used for disease modification requires a means of getting to the central nervous system. Today, drugs
in phase II clinical trials are administered directly into the central nervous system, either intrathecally into the lumbar CSF, intraparenchymally or intraventricularly.

The use of ASOs is another important future therapeutic goal for disease modification of HD, recently published after a successful phase I-IIa study by Tabrizi, Leavitt, et al. (2019). Intrathecal administration of ASOs in patients with early stages of HD showed a dose-dependent reduction in the concentration of mHTT, and is now due to go into phase III clinical trials (Tabrizi, Leavitt, et al., 2019). The response from the HD community has been positive towards this drug being used as a future disease modifying treatment, but results from the phase III clinical trials will only show with time. If the results for the phase III clinical trial are positive, the future for HD patients will look optimistic. One question will then emerge: “At which age should treatment be available for HD patients?” This is important for future research in the fields of diagnostic and premanifestation staging of the disease. Once we have both a disease modifying treatment and the right premanifestation time to initiate the treatment, the fear of losing oneself to this devastating disease will hopefully disappear.
7. Material and Methods

Search criteria and strategy

A search of the databases PubMed and MeSH was conducted 06.12.2019 and 06.01.2020 to identify relevant literature published of Huntington’s disease published between 1966 and January 2020. These dates were selected in order to include all published literature, and specific inclusion criteria were used to narrow the number of papers to include. Textbooks in neurology, neurosurgery and neuroanatomy were also included. The search strings used included key words related to (1) species of interest, i.e. human; (2) the disease of interest, i.e. Huntington’s disease; (3) article type should be review; and (4) papers should include one of the different subheadings of interest, i.e. history, classification, pathology and pathophysiology, diagnostic, complications and mortality, treatment and therapy, molecular mechanisms, genetics and epigenetics, and epidemiology. The different subheadings included several key words, and the PubMed MeSH results for each of the subheadings are shown in Figure 4. See Supp.File 1 for search strings used for the literature search.

Studies and papers were included if they satisfied all of the following criteria: (1) published in peer-reviewed journals, (2) written in English, (3) were available to read or in pdf format, (4) was a review, (5) included at least some self-defined key words in regards to the different subheadings. The MeSH search provided in total of 3030 results that were eligible for abstract review. All titles, abstracts and authors keywords were reviewed manually, and papers were included based on the several inclusion criteria and self-defined key words. Self-defined key words were chosen on the basis of the most common key words present in all papers.

Due to relevance of the papers of George Huntington, Johan Christian Lund, Waters and Vale, although these did not appear in the MeSH search, these were included to give an overview of the early history of Huntington’s disease. The relevance of clinical trials also resulted in these being included to give an overview of the recent and ongoing trials in the therapy of Huntington’s disease.

To limit the selection of papers and thus the scope of the survey, papers that did not relate to Huntington’s disease and the various subheadings were excluded. I also excluded papers that reviewed a group of neurodegenerative disorders unitedly, or that did only have a small paragraph about Huntington’s disease interspersed with other disorders or syndromes. Papers not in English or where I did not have access to the paper were automatically excluded.
An interview with Dr.med Lasse Philstrøm was conducted in January 2020. Dr.med Lasse Philstrøm is the HD coordinator at the department of neurology at Rikshospitalet, and is responsible for all HD patients referred to Oslo University Hospital. The interview included a clinicians view of the health care delivery practice for HD patients in Norway, from when the patients starts seeking medical help, through their journey with diagnosis and treatment, until palliative care and admission to a nursing home is initiated.

Figure 4 Flow chart of PubMed MeSH study selection for this assignment.
References


Lund, J. C. (1860). Chorea Sti Viti I Seterdalen. [Beretning om Sundhetsstilstanden m.m. i Norge.


Supplementary File 1 Search string used for literature search

"Huntington Disease/history"[Mesh] AND Review[ptyp]

"Huntington Disease/classification"[Mesh] AND Review[ptyp]

"Huntington Disease/anatomy and histology"[Mesh] OR "Huntington Disease/embryology"[Mesh] AND Review [ptyp]


"Huntington Disease/complications"[Mesh] OR "Huntington Disease/mortality"[Mesh] AND Review [ptyp]


"Huntington Disease/genetics"[Mesh] AND Review[ptyp]

("Huntington Disease/economics"[Mesh] OR "Huntington Disease/epidemiology"[Mesh] OR "Huntington Disease/organization and administration"[Mesh] OR "Huntington Disease/statistics and numerical data"[Mesh]) AND Review[ptyp]
# Supplementary File 2 The Unified Huntington’s Disease Rating Scale (UHDRS)

## Motor assessment

<table>
<thead>
<tr>
<th></th>
<th>Rating scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ocular pursuit (horizontal and vertical)</td>
<td>Complete (normal)</td>
</tr>
<tr>
<td>Saccade initiation (horizontal and vertical)</td>
<td>Normal</td>
</tr>
<tr>
<td>Saccade velocity (horizontal and vertical)</td>
<td>Normal</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Normal</td>
</tr>
<tr>
<td>Tongue protrusion (right and left)</td>
<td>Can hold tongue fully protruded for 10 seconds</td>
</tr>
<tr>
<td>Maximal dystonia (trunk and extremities)</td>
<td>Absent</td>
</tr>
<tr>
<td>Maximal chorea (face, mouth, trunk and extremities)</td>
<td>Absent</td>
</tr>
<tr>
<td>Retropulsion pull test</td>
<td>Normal</td>
</tr>
<tr>
<td>Finger taps (right and left)</td>
<td>Normal &gt; 15/5 sec</td>
</tr>
<tr>
<td>Pronate/supinate hands (right and left)</td>
<td>Normal</td>
</tr>
<tr>
<td>Luria (fist-hand-palm test)</td>
<td>&gt;4 in 10 seconds, no cue</td>
</tr>
<tr>
<td>Rigidity-arms (right and left)</td>
<td>Absent</td>
</tr>
<tr>
<td>Bradykinesia-body</td>
<td>Normal</td>
</tr>
<tr>
<td>Gait</td>
<td>Normal gait, narrow base</td>
</tr>
<tr>
<td>Tandem walking</td>
<td>Normal for 10 steps</td>
</tr>
</tbody>
</table>

## Cognitive assessment

### Verbal fluency test (raw score)

### Symbol digit modalities test (raw score)
### Stroop interference test
- Color naming (number correct)
- Word reading (number correct)
- Interference (number correct)

### Behavioral assessment

<table>
<thead>
<tr>
<th>Severity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = absent</td>
<td>0 = almost never</td>
</tr>
<tr>
<td>1 = slight, questionable</td>
<td>1 = seldom</td>
</tr>
<tr>
<td>2 = mild</td>
<td>2 = sometimes</td>
</tr>
<tr>
<td>3 = moderate</td>
<td>3 = frequently</td>
</tr>
<tr>
<td>4 = severe</td>
<td>4 = almost always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sad mood</td>
<td>Feeling sad, sad voice/expression, tearfulness, inability to enjoy anything</td>
</tr>
<tr>
<td>Low self-esteem/guilt</td>
<td>Self blame, self depreciation including feelings of being a bad or unworthy person, feelings of failure</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Worries, anticipation of the worst, fearful anticipation</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Feels life not worth living, has suicidal thoughts, active suicidal intent, preparation for the act</td>
</tr>
<tr>
<td>Disruptive or aggressive behavior</td>
<td>Threatening behavior, physical violence, verbal outbursts, threatening, foul, or abusive language</td>
</tr>
<tr>
<td>Irritable behavior</td>
<td>Impatient, demanding, inflexible, driven and impulsive, uncooperative</td>
</tr>
<tr>
<td>Obsessions</td>
<td>Recurrent and persistent ideas, thoughts or images</td>
</tr>
<tr>
<td>Compulsions</td>
<td>Repetitive, purposeful, and intentional behaviors</td>
</tr>
<tr>
<td>Delusions</td>
<td>Fixed false beliefs, not culturally shared</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>A perception without physical stimulus: auditory, visual, tactile, gustatory and olfactory?</td>
</tr>
</tbody>
</table>

### Ask questions
- Does the investigator believe the subject is confused? Yes or No
- Does the investigator believe the subject is demented? Yes or No
- Does the investigator believe the subject is depressed? Yes or No
- Does the subject require pharmacotherapy for depression? Yes or No

### Functional assessment

<table>
<thead>
<tr>
<th>Task</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could subject engage in gainful employment in his/her accustomed work?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject engage in any kind of gainful employment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject engage in any kind of volunteer or non gainful work?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject manage his/her finances (monthly) without any help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject shop for groceries without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject handle money as a purchaser in a simple cash (store) transaction?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject supervise children without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject operate an automobile safely and independently?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject do his/her own housework without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject do his/her own laundry (wash/dry) without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject prepare his/her own meals without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject use the telephone without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject take his/her own medications without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject feed himself/herself without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject dress himself/herself without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject bathe himself/herself without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject use public transportation to get places without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject walk to places in his/her neighborhood without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject walk without falling?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject walk without help?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could subject comb hair without help?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Could subject transfer between chairs without help?  
Could subject get in and out of bed without help?  
Could subject use toilet/commode without help?  
Could subject’s care still be provided at home?  

### Independence scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>No special care needed</td>
</tr>
<tr>
<td>090</td>
<td>No physical care needed if difficult tasks are avoided</td>
</tr>
<tr>
<td>080</td>
<td>Pre-disease level of employment changes or ends; cannot perform household chores to pre-disease level, may need help with finances</td>
</tr>
<tr>
<td>070</td>
<td>Self-care maintained for bathing, limited household duties (cooking and use of knives), driving terminates; unable to manage finances</td>
</tr>
<tr>
<td>060</td>
<td>Needs minor assistance in dressing, toileting, bathing; food must be cut for patient</td>
</tr>
<tr>
<td>050</td>
<td>24-hour supervision appropriate; assistance required for bathing, eating, toileting</td>
</tr>
<tr>
<td>040</td>
<td>Chronic care facility needed; limited self feeding, liquefied diet</td>
</tr>
<tr>
<td>030</td>
<td>Patient provides minimal assistance in own feeding, bathing, toileting</td>
</tr>
<tr>
<td>020</td>
<td>No speech, must be fed</td>
</tr>
<tr>
<td>010</td>
<td>Tube fed, total bed care</td>
</tr>
</tbody>
</table>

### Functional capacity

<table>
<thead>
<tr>
<th>Score</th>
<th>Occupation</th>
<th>Finances</th>
<th>Domestic chores</th>
<th>ADL</th>
<th>Care level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unable</td>
<td>Unable</td>
<td>Unable</td>
<td>Total care</td>
<td>Full time skilled nursing</td>
</tr>
<tr>
<td>1</td>
<td>Marginal work only</td>
<td>Major assistance</td>
<td>Impaired</td>
<td>Gross tasks only</td>
<td>Home or chronic care</td>
</tr>
<tr>
<td>2</td>
<td>Reduced capacity for usual job</td>
<td>Slight assistance</td>
<td>Normal</td>
<td>Minimal impairment</td>
<td>Home</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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