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Cognition in Huntington's Disease

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1. Introduction

Huntington's Disease (HD) is an autosomal dominant, neurodegenerative disease. It is characterized by severe involuntary motor dysfunction, so-called choreic movements, neurological and psychiatric symptoms and cognitive impairments that lead to dementia (Bates et al., 2002). Genetic markers for the gene that causes HD were identified in 1983, located on the short arm of chromosome four (Gusella et al., 1983). Ten years later in 1993 the gene was cloned (Huntington's Disease Collaborative Research Group, 1993). HD was thus from the mid-1980s one of the first diseases where it was possible to predict whether an asymptomatic individual had inherited the genetic markers and would therefore become ill in the future. The clinical diagnosis of HD is based on the presence of motor symptoms and a positive mutation analysis, or on neurological and psychiatric symptoms in patients with a family history of HD.

In almost half of HD cases clinical onset is indicated with psychiatric symptoms such as depression, anxiety and aggressive outbursts (Close Kirkwood et al., 2002a; Julien et al., 2007; van Duijn et al., 2007). Sometimes onset of the disease presents with schizophrenic or manic-like symptoms (Julien et al., 2007; Shiwach, 1994). However, the initial indication of onset is often in the form of subtle cognitive impairment before manifest neurological or psychiatric symptoms occur. All patients become demented over the course of the disease (Brandt et al., 1984). The first symptoms occur most frequently in the 45 to 50 age bracket, although age of onset ranges from 2 to 80 years (Roos et al., 1991). The average life expectancy after clinical onset is 15-17 years (Roos et al., 1993). In the juvenile form of Huntington's Disease onset occurs before age 20 (5-10% of cases) and approximately 25% of HD debuts after age 50, some at age 70 or older (Kremer, 2002). There is currently no specific treatment to cure or delay the disease.

2. General aspects of the disease

2.1 Nomenclature

Huntington's Disease has been described in varying ways throughout history. Christian Lund described HD or Anundsjö disease in Norwegian in 1860 (Orbeck, 1960) and a young American doctor, George Huntington, published a description of HD in 1872 which is still

largely valid (Huntington, 1872). The disease has since carried his name and is also called Huntington's Chorea (from the Greek, χορός, dance and khoreia, chorea). The Westphal variant of Huntington's Disease manifests in muscular rigidity and hypokinesia in young adults, usually between 20-30 years. The correct term today is Huntington's Disease.

2.2 Prevalence

The prevalence of HD in many countries is not established and estimates differ considerably from country to country (Harper, 2002). The prevalence in Western Europe is estimated at approximately 3-7 per 100 000 depending on city and country. For example, the prevalence is well mapped in England and varies in the range 2.5-9.95 per 100 000 (Harper, 2002). North American prevalence is estimated at 4.1 to 8.4 per 100,000 inhabitants. Many countries have no information or only sporadic information on the prevalence of HD. The prevalence is lower among indigenous populations in Africa (e.g. 0.01 per 100 000 in South Africa) and Asia (0.7 per 100 000 in Japan and 0.4 per 100 000 in Hong Kong). Areas with notably high prevalence of HD are found in Tasmania, Australia (17:100 000) (Conneally, 1984) and in the Lake Maracaibo district of Venezuela (Young et al., 1986).

2.3 Cause and heredity

HD (OMIM 143100) is an autosomal dominant neurodegenerative disease caused by a mutation in the short arm of chromosome 4 (4p16.3) (Gusella et al., 1983) (Figure 1).

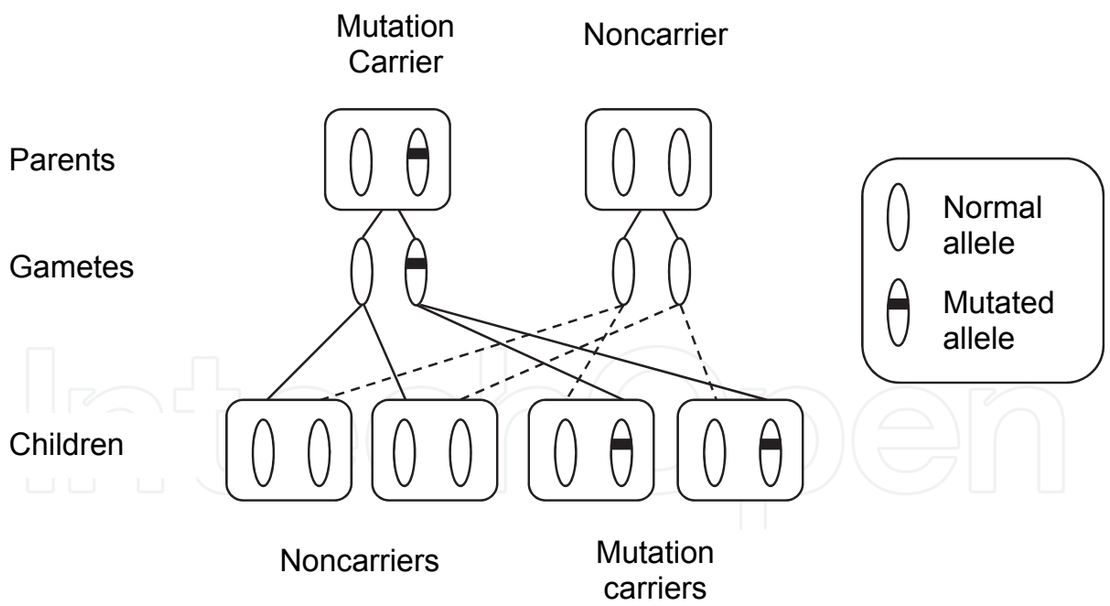

Fig. 1. Autosomal dominant inheritance

2.4 CAG sequences

A mutation in the huntingtin (HTT) gene causes an increase in the number of trinucleotide CAG (Cytosine, Adenosine, Guanine) repetitions, always 36 or more for individuals with HD (Huntington's Disease Collaborative Research Group, 1993). A person with normal

function has between 9 and 35 repetitions of the CAG sequence. Repetitions from 36 to 39 are characterized by reduced penetrance, therefore an individual in this range will not automatically develop the characteristic symptoms of HD during his lifetime, but children of such an individual are still at risk (Rubinsztein et al., 1996). A sequence of 40 CAG repetitions or more has full penetrance. There is also a negative correlation between the number of CAG repetitions and age at onset, but this does not explain all variation in the age at onset, which means that other factors possibly interact and determine when disease symptoms will appear (see table 1).

CAG sequences	
≤ 28	Normal function
29-35	The individual will not develop HD, but the next generation inherits the risk of developing the disease.
36-39	Reduced penetrance; some individuals will develop HD and development is generally late in life. The next generation inherits the risk of developing the disease. A number of non-symptomatic cases in older individuals with 36-39 CAG sequences have been reported.
≥ 40	Full penetrance; all individuals will develop the disease. Higher CAG sequences provides earlier disease onset (negative correlation). Juvenile HD manifests itself most often in people with ≥ 60 CAG repetitions.

Table 1. Number of CAG sequences and risk of onset.

The number of CAG repetitions tends to be extended at the formation of the sex cells and takes place primarily when the gene is inherited from the father (Kehoe et al., 1999). Inheritance via the male line leads to cases of earlier onset and also more deleterious disease outcome, so called anticipation (Ridley et al., 1988). Estimated age at onset can be calculated using a regression equation, although not always accurately (Langbehn et al., 2004; Langbehn et al., 2009; Rubinsztein et al., 1997). Spontaneous mutations are very rare and explain only 0.1 % of the cases of the disease. However, it is reported that about 8% of HD patients do not have an affected family member (Almqvist et al., 2001; Siesling et al., 2000).

2.5 Neuropathological changes

A widespread, selective neuropathology is found in HD, with cell loss and atrophy. The changes are strikingly selective in their effect on specific brain cell types and particular brain structures. Medium γ-aminobutyric acid (GABA) spiny neurons are the neuronal cells primarily affected, mainly in the caudate nucleus and putamen. The cortex is less affected and the cerebellum is relatively spared. The HD gene product, a very large 350 kDa protein, termed *huntingtin*, is believed to have a toxic effect which leads to cellular dysfunction and eventual death of neurons (Huntington's Disease Collaborative Research Group, 1993). The exact mechanism of the toxic effect is still poorly understood. Early neuropathological changes are seen selectively in the striatum, where 90% of neuronal cells are medium spiny projection neurons (MSP neurons). Loss of projection neurons in the caudate nucleus is the dominant neuropathological change. Death of neuronal cells continues gradually in layers 3, 5 and 6 of the cortex, the substantia nigra and the CA1 region of the hippocampus. Loss of enkephalin-withholding MSP neurons in the striatum, which indirectly controls voluntary

and related movements, constitutes the neurobiological basis for HD chorea. The preferential involvement of the indirect pathway of basal ganglia-thalamocortical circuitry is believed to be the cause of chorea (Paulsen et al., 2005a). Fronto-striatal circuitry linking the striatum with frontal lobes is also affected. In addition, changes in the substantia nigra, hippocampus, hypothalamus and selectively in the cortex and white matter are found.

2.6 Chemical changes

Profound atrophy in large parts of the brain is seen in the final stage of the disease. Neuronal loss leads to reduction of neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, glutamic acid decarboxylase (GAD), peptides (e.g. enkephalin) and acetylcholine (choline acetyltransferase, ChAT) in the striatum. On the other hand, there are increases in serotonin levels, while serotonin receptor density decreases. A reduction in postsynaptic D_1 and D_2 dopamine receptors and in the dopamine transporter DAT in the striatum also has the potential to explain the cognitive impairments of HD patients (Antonini et al., 1996; Backman et al., 1997). The complex and multifarious symptoms of HD have been attributed to these neuropathological and neurochemical changes (Walker, 2007).

3. Clinical picture and progress

3.1 Clinical picture

The clinical picture includes severe motor dysfunction, cognitive decline leading to dementia and neurological and psychiatric symptoms. Symptoms of HD vary from patient to patient and although all symptoms may be present, some symptoms are more dominant during different phases. Cognitive impairments occur early in the disease, exacerbated when manifest disease progresses and causes reductions in everyday functions. Affected cognitive domains include psychomotor speed, language, memory and executive functions; and later in the disease visuospatial abilities are also affected (Robins Wahlin et al., 2010; Robins Wahlin et al., 2007).

3.2 Motor symptoms

Severe locomotor dysfunction with hyperkinesia characterizes HD. These involuntary movements are seen first in the fingers and toes, then in the trunk. Approximately 10% of all patients with HD may, however, have the juvenile onset or Westphal variant of HD with symptoms of hypokinesia and rigidity similar to Parkinson's disease (Bittenbender & Quadfasel, 1962; Bruyn, 1962). Difficulties with balance occur, with exaggerated, fidgeting motor action and a tendency to violent involuntary movements. HD patients often walk with a dance-like gait with legs widely separated to compensate for the lack of balance and control. The symptoms may cause the patient to appear to be intoxicated by alcohol. Almost all patients manifest irregularly timed, randomly distributed and abrupt choreatic movements (Barbeau et al., 1981). They may keep their hands in their pockets to limit uncontrollable arm actions. Facial musculature is also affected with characteristic chorea of the face showing in the form of pouting of the lips, lifting of the eyebrows, frowning and nodding head movements. Eye movements become disturbed at an early stage, with jerky action and the patient has difficulty focusing the eyes on moving objects. Fine motor skills decline, characterized by clumsiness and problems with grasping and holding objects. A

patient may be diagnosed when subtle neurologic symptoms are identifiable as disturbed tongue and eye movements. Dysarthria is found early, while dysphasia is common in the final stage. For about half of patients the extrapyramidal motor symptoms manifest at clinical onset (Mattsson, 1974). Patients with later age of onset, 50-70 years of age, debut with involuntary movements, walking difficulties and dysphasia. These patients usually have a slower and more benign development of the pathological processes compared with patients with a younger age of onset (see Table 2).

Prodromal phase — Early Signs	**Manifest and clinical phase -- Signs & symptoms**	**Dementia Phase -- Late in the disease**
Agitation Egocentricity, persistence	Myotonic dystrophy Myoclonus Problems initiating movements	Rigidity Decreasing involuntary movements
Irritability, aggressiveness, anger	Increasing involuntary movements	Grave or diminishing chorea
Apathy	Choreatic manifestations; writhing, jerky movements	Increase in falls
Anxiety	Balance and gait difficulty	Inability to walk
Uninhibited behaviour	Problems with fine motor skills (such as shoe-laces)	Developmental Dyspraxia
Impaired impulse control	Problem with swallowing; danger of inhalation	Dysphagia
Euphoria	Slowed voluntary movements	Bradykinesia
Abnormal eye movements	Inability to control the speed and force of movements, clumsiness	Difficulty in swallowing & eating
Sadness	Dyskinesia	Neglected nutrition
Depression	General weakness	Wheelchair bound
Suicidal Ideation	Weight loss	Weight loss
Slowness of speech	Speech impairments; slurred speech & phonological impairment, difficulty with pronunciation	Dysphasia, serious speech impairments, mutism
Motion	Problems with daily living activities (ADL)	Inability to manage ADL
Psychological denial	Muscle stiffness	Incontinence
Symptom searching (mutation carriers)	Delusions, hallucinations	Evident regression

Table 2. Clinical signs and symptoms.

3.3 Behavioural changes and psychiatric disorders

About half of patients debut with affective disorders or psychiatric symptoms (Mattsson, 1974). These may occur before other clear symptoms manifest and can be very difficult to manage. They sometimes dominate the clinical picture. Around 72-98% of HD individuals develop significant neuropsychiatric problems, including both affective psychoses and non-

affective psychoses (Mendez, 1994; Paulsen et al., 2001; van Duijn et al., 2007). Major depression (Larsson et al., 2006) and manic episodes also occur (van Duijn et al., 2008). In the manic phase, presentation is the same as for bipolar disorder. As Huntington noted, socially deviant behavior occurs when the individual fails to recognize or register their divergent behavior (Huntington, 1872). Hallucinations of hearing, smell, sight, taste and touch may be present in HD. The most common neuropsychiatric symptoms are reported to be dysphoria (69%), agitation (67%), irritability (65%), apathy (56%), anxiety (52%), disinhibition (35%) and euphoria (31%) (Paulsen et al., 2001). The unusually diverse manifestations of the disease have made diagnosis difficult to determine, especially before DNA testing (Tost et al., 2004)(see Table 2).

3.4 Depression

General sadness, depression and anxiety are frequently displayed early in the disease course (Larsson et al., 2006). Apathy and irritability (33% to 76%) are also amongst the first symptoms (van Duijn et al., 2007). When depression occurs it is often characterized by hopelessness, guilt and shame (Baudic et al., 2006; Kessler, 1987). The suicide rate in people with HD is twice that of the normal population (Robins Wahlin et al., 2000) and suicide risk is highest in the context of disease onset (Paulsen et al., 2005b). It is not known whether depression is an integral part of the disease or a response to the knowledge of the severity of the disease in the patient's future, or possibly a combination of the two. The affective disorder may be an explicit manifestation of brain damage. Depression can also be an expression of grief and anxiety, as HD patients are aware that their children may await the same fate that they are facing (Bird, 1999; Paulsen et al., 2001).

3.5 Cognitive impairments and dementia

The cognitive symptoms of HD vary from patient to patient and although several symptoms can be present, some dominate more than others through the different phases (see Table 3). Cognitive signs manifest early in the disease, exacerbated when manifest disease progresses causing reduced ability to perform everyday functions. Affected cognitive domains include psychomotor speed, language, memory, executive functions and later also visuospatial abilities (Lawrence et al., 2000; Robins Wahlin et al., 2010; Robins Wahlin et al., 2007; Snowden et al., 2002; Stout et al., 2011). The cognitive deterioration can be divided into three main phases, depending on the disease progress: prodromal phase, clinical phase and dementia phase. The cognitive phases are associated with reductions in the total functional capacity (Total Functional Capacity scale, TFC) in the areas of occupational activity, finances, domestic chores, activities of daily living (ADL) and increasing care needs (Beglinger et al., 2010; Paulsen, 2010; Shoulson & Fahn, 1979).

4. The prodromal phase

4.1 The prodromal phase and early signs

Neurological symptoms may not be detected in this phase and therefore it is called the prodromal, preclinical or presymptomatic phase. Patients often report memory difficulties, concentration and attention problems or psychosomatic symptoms before the disease can be diagnosed definitively (Verny et al., 2007). Changes in behavior in relation to either family or

friends are very subtle. Increasing difficulty managing emotions sometimes leads to aggressive outbursts in surroundings where the outbursts may not seem warranted. These are sometimes referred to as "catastrophic reactions" (Almqvist et al., 1999). Patients may seek out physicians due to stress or psychosomatic symptoms such as gastrointestinal problems or insomnia, which need symptomatic treatment. Difficulties arise in managing tasks at home and work and such difficulties are only understood with hindsight after diagnosis.

Prodromal phase — Early signs	**Manifest and clinical phase - Sign & symptoms**	**Dementia Phase -- Late in the disease**
Psycho-motor slowness ▼ ▼	Clear psycho-motoric slowness ▼ ▼ ▼	Impaired cognitive functions ▼ ▼ ▼
Executive functions: Concentration ▼ Initiation ▼ ▼ Attention ▼ Flexible thinking ▼ Logical thinking ▼ Simultaneous capacity▼ Judgement▼	Executive functions: Concentration ▼ ▼ Initiation ▼ ▼ ▼ Attention ▼ ▼ Flexible thinking ▼ ▼ Logical thinking ▼ ▼ Simultaneous capacity ▼ ▼ Judgement ▼ ▼	Executive functions: Concentration ▼ ▼ ▼ Initiation▼ ▼ ▼ Attention ▼ ▼ ▼ Flexible thinking ▼ ▼ ▼ Logical thinking ▼ ▼ ▼ Simultaneous capacity ▼ ▼ ▼ Judgement ▼ ▼ ▼
Slightly impaired verbal flow ▼	Markedly impaired verbal flow ▼ ▼	Impaired verbal flow or mutism ▼ ▼ ▼
Declining working memory ▼ ▼	Clearly impaired working memory ▼ ▼ ▼	Greatly impaired working memory ▼ ▼ ▼
Reductions in episodic memory: Encoding▼ Retrieval; search strategies▼ Learning ▼ ▼ Recognition (minor problem)	Significant reductions in episodic memory: Encoding ▼ ▼ Retrieval; search strategies ▼ ▼ Learning ▼ ▼ ▼ Recognition ▼	Severe reductions in episodic memory: Encoding ▼ ▼ ▼ Retrieval; search strategies ▼ ▼ Learning ▼ ▼ ▼ Recognition ▼ ▼
Prospective memory difficulties (remember appointments) ▼	Prospective memory difficulties (forgets to pay bills) ▼ ▼	Inability to access prospective memory ▼ ▼ ▼
Mild visuospatial difficulties ▼	Notable visuospatial difficulties ▼	Greatly reduced visuospatial ability ▼ ▼

▼ Mild signs and symptoms; ▼ ▼ Moderate disturbance; ▼ ▼ ▼ Grave disorder

Table 3. Neuropsychological characteristics in Huntington's Disease.

4.2 The prodromal cognitive disorder

The first cognitive changes occur approximately 12-15 years before clinical (motor) onset of the disease (Paulsen et al., 2008; Robins Wahlin et al., 2007; Stout et al., 2011). These prodromal changes are characterized by reduced executive functions which present as alterations in flexibility, reasoning and verbal fluency (Larsson et al., 2008). Lack of logical thinking and difficulties in the skills of decision-making, initiative, attention and planning are very early signs (Lemiere et al., 2004; van Walsem et al., 2009). The ability to conduct complex reasoning, to perform tasks in sequence and to demonstrate simultaneous capacity

(dual tasking) all deteriorate gradually (Stout et al., 2011). Linguistic features work relatively well, but syntactic complexity and verbal fluency decrease (Larsson et al., 2008). Working memory and attention show early impairments (Verny et al., 2007). Episodic memory impairment begins with active learning difficulties and inability to apply effective search strategies for information (Montoya et al., 2006a; Solomon et al., 2007; Verny et al., 2007). Memory tasks where only recognition is required exhibit better performance, suggesting a greater problem with retrieval than with encoding of information. Learning new skills becomes more difficult and takes longer (see Figure 2) (van Walsem et al., 2009; Verny et al., 2007). Reduced learning ability and concentration cause problems in occupational, financial and domestic functioning. Mutation carriers in the prodromal phase may need to be referred for comprehensive neuropsychological assessment to determine their capacity for employment, driving of motor vehicles and decision-making (Beglinger et al., 2010).

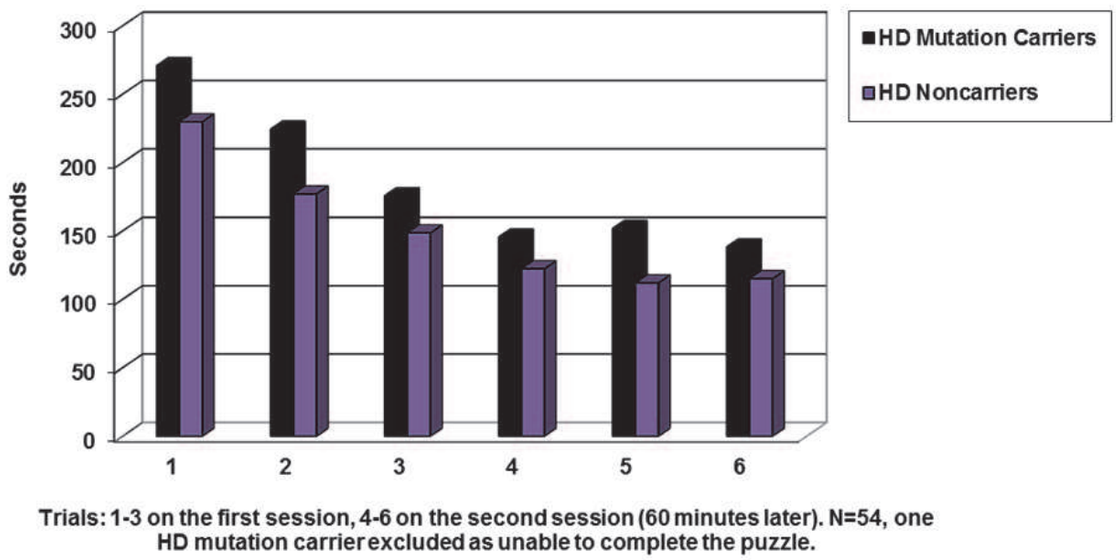

Fig. 2. Performance time on the Tower of Hanoi Puzzle Across Huntington's Disease Groups (Robins Wahlin et al., 2007).

5. Clinical phase

5.1 Clinical neurological and psychiatric disorder

In the clinical phase the neurological symptoms emerge, including the involuntary movements that are characteristic of HD. Many patients lose weight, despite maintaining or sometimes even increasing their food intake. The motor symptoms vary in intensity depending on the degree of mental tension and activation. At the beginning of the clinical phase the involuntary movements are so subtle that patients do not notice them. Later on, usually after about 10 years, the chorea causes grave disability. Over this period there is also a marked decline in executive functioning and a diminishing ability to get organized in everyday situations (Paulsen, 2010; Paulsen et al., 2001). Thinking skills and social and emotional functioning deteriorate. Depression, social isolation and denial of symptoms (anosognosia) are characteristic also in this phase. The critical period for suicide is precisely

connected with the stage of illness (Paulsen et al., 2005a) when understanding is maintained and the disease's debilitating symptoms are seen as a threat for the future. Cognitive slowness in combination with reduced attention and failure to notice or correct errors eventually cause the patient to lose their driving licence and their employment (Beglinger et al., 2010). The behavioral problems lead to increased impulsivity, aggressiveness and sometimes even hypersexuality. Marital relationships are commonly strained.

5.2 Clinical cognitive disorder

As the disease progresses, neuropsychological skills requiring executive functioning deteriorate further, including skills such as concentration, patience and stamina. Reduced ability for abstract thinking becomes more apparent and the patient exhibits a greater degree of concrete thinking. Judgment, discrimination and ability to plan are increasingly reduced. Sometimes the patient becomes apathetic. Their semantic memory is initially only slightly reduced (Robins Wahlin et al., 2010) and they continue to recognize close relatives and familiar surroundings. On the other hand, episodic and prospective memory decline, for example remembering future tasks such as appointments (Lundervold et al., 1994b). Working memory continues to deteriorate. Memory deficits consist of a generalized impaired ability to learn new information and retrieve old knowledge, in other words learning curves show a low, flat line (Butters et al., 1994; Verny et al., 2007). Phonemic and semantic fluency becomes decidedly slower (e.g. FAS and categories). Vocabulary decreases, the patient becomes taciturn, distinctions in meaning are lost and the patient has difficulty keeping up with discussions. Because parietal functions are connected to the striatum, visuospatial difficulties are manifested at this stage (Lundervold & Reinvang, 1991). Deteriorating visuospatial skills as well as psychomotor slowness create major difficulties and patients at this stage are strongly advised not to drive a car. Reductions in visuospatial functions can be tapped by missed details and distorted relationships when the patient copies shapes (e.g. Rey-Osterrieth Complex Figure, see Figure 3 and 4) (Osterrieth, 1944; Rey, 1941).

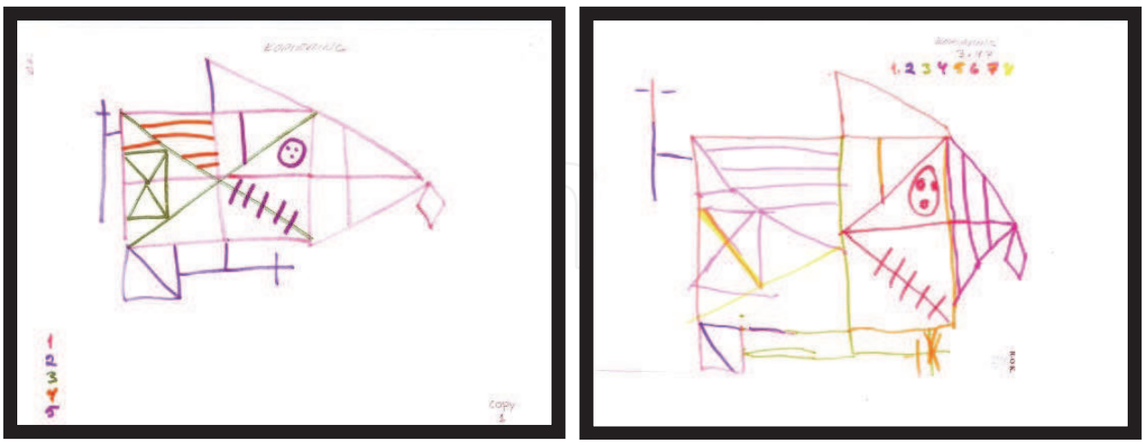

Fig. 3. and 4. Examples of organized (left panel) and disorganized (right panel) Rey-Osterrieth Complex Figures (ROCF) as copied by mutation carriers of HD. The left ROCF was drawn by a female mutation carrier with nine years to estimated disease onset and the ROCF right figure was drawn by a female carrier with one year to estimated disease onset, although the latter patient had not yet been diagnosed by a neurologist as having manifest HD.

6. Dementia phase

6.1 The neuropsychiatric disorder in dementia phase

Dementia symptoms in HD differ in part from what is seen in other dementias such as Alzheimer's disease in that the three great "As" (Aphasia, Apraxia, Agnosia) do not dominate in the early symptomatic stage, however, these symptoms manifest in the dementia phase. Increasing dementia expresses in passivity, loss of non-verbal communication and increasing apathy. Lack of awareness of loss of ability frequently occurs. Patients with HD are extremely slow and restricted in both movement and speech during the depressive and apathetic phases (Paulsen et al., 2001). Lack of initiative may cause them to cease taking care of their own health and hygiene. The sleep cycle is often disturbed, probably because of hypothalamic dysfunction (Soneson et al., 2010). Explosive eruptions occur, with emotional lability and even catastrophic reactions requiring extra resources from daily caregivers (Almqvist et al., 1999; Decruyenaere et al., 2005). In the final stage of the disease, the patient is often bedridden, has lost nearly all functions in everyday activities and is in need of 24 hour care (Zakzanis, 1998).

6.2 Cognitive disturbance in dementia phase

All intellectual functions are severely reduced in the final stage (Lundervold et al., 1994a; Zakzanis, 1998). Inability to mobilize knowledge combined with a lack of motivation presents as generalized dementia (Redondo-Verge, 2001). Evidence of general intellectual sluggishness and semantic slowness is substantial. It may take up to one minute to express a word or idea. As the disease progresses, speech and linguistic ability becomes increasingly difficult and eventually the patient may become mute. Severe dementia is dominant in the final stage (Zakzanis, 1998).

6.3 Psychological and practical implications

HD is often associated with shame and guilt. The disease is viewed as a problematic psychiatric disease because early cognitive and psychiatric symptoms produce abnormal behavior (Paulsen et al., 2001; Robins Wahlin et al., 2000). Symptoms of chorea (involuntary movements) have relatively little impact on the person's functional ability, but unfortunately attract attention and often give the wrong impression that the patient is intoxicated. Neurological signs such as unsteadiness, grimacing and twitching of the face and symptoms of mental illness may be seen as shameful by the victim and his family. Stories about patients being hidden, rejected or repudiated exist in many families. Many times the disease is a great family secret and associated with a lot of denial (Deckel & Morrison, 1996). There is a fear of contracting the disease and its insidious onset leads to intense trawling for early signs which can then be interpreted as symptoms that the manifest phase has begun (Robins Wahlin, 2007).

7. Assessment and diagnosis

7.1 The neuropsychological assessment

Verbal episodic memory, working memory, executive function, verbal fluency and psychomotor speed should be investigated early in the prodromal phase of HD as impairments occur before manifest symptoms are visible (Kirkwood et al., 2000; Verny et al.,

2007). A simple test battery is recommended that includes tests of a variety of cognitive abilities including verbal fluency and memory tasks. The Unified Huntington's Disease Rating Scale (UHDRS) is specially developed for HD and contains a brief cognitive test battery (Huntington Study Group, 1996). The UHDRS is designed to be administered each time the patient comes to follow-up appointments. UHDRS takes approximately 30-45 minutes to implement and includes the following neuropsychological tests which are relatively simple to administer.

1. Letter Fluency (Phonemic) Controlled Oral Word Association Test (COWAT, FAS)
2. Dementia Rating Scale
3. Hopkins Verbal Learning Test (HVLT)
4. Symbol Digit Modalities Test (Digit Symbol in Wechsler Adult Intelligence Scale, WAIS).
5. Stroop Test.
   (a) Colour Naming
   (b) Word Reading
   (c) Interference
6. Trail Making Test A & B
7. Category Fluency (Semantic) Animals

If there is insufficient time for the entire test battery, assessment can be shortened to 10-15 minutes by examining verbal fluency (FAS, animals, see Figures 5 and 6), speed and executive functions (Symbol Digit, Stroop Test, TMT A & B) (Lezak et al., 2004; Strauss et al., 2006). The full test battery is suitable for annual examination which track the mutation carrier's functional levels for employment and holding a driver's licence while in the prodromal phase. Learning effects of the UHDRS are minimal, except for the HVLT, which is available in six parallel versions (Beglinger et al., 2010; Brandt & Benedict, 2001). The HVLT consists of an episodic memory task with 12 words, with four words from each of three semantic categories. The parallel versions avoid learning effects in annual patient evaluations (Solomon et al., 2007; Woods et al., 2005).

7.2 In-depth clinical neurological/neuropsychological examination

In recent years, quantified neurological examinations (Folstein et al., 1983) have been supplemented and/or replaced by the Unified Huntington's Disease Rating Scale (UHDRS) for examination of motor functions in HD (Huntington Study Group, 1996). The Total Functional Capacity (TFC) scale is used internationally as a neurological functional scale that includes areas such as activities of daily living (ADL), occupational activities, financial management, living chores and care needs (Paulsen et al., 2010; Shoulson & Fahn, 1979). The total functional scale (0-13) score correlates highly with cognitive and motor impairments (Kremer, 2002). Great care is needed in the selection of neuropsychological test battery instruments, in order to ensure high sensitivity in detecting prodromal evidence of HD. Although there are now a number of published studies of cognitive impairment in prodromal HD, it has not yet been established whether there is a characteristic pattern of impaired cognitive function prior to the onset of the motor symptoms of HD. Two studies report a pattern of prodromal cognitive function and intelligence as measured by the Wechsler Adult Intelligence Scale (Wechsler, 1997), with Robins Wahlin reporting significant differences in functioning across the various WAIS-R subtests and Verbal, Performance and Full Scale IQ scores (see Figure 7 and 8) (de Boo et al., 1997; Robins Wahlin et al., 2010).

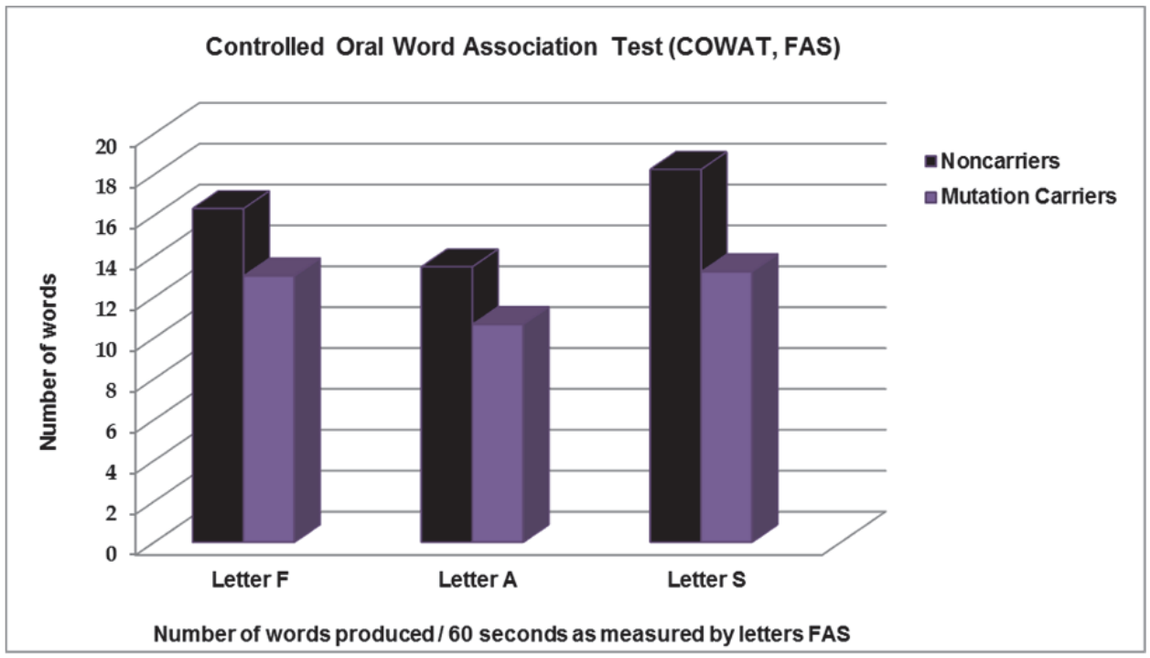

Fig. 5. Phonemic fluency as measured by the letters FAS in a Swedish sample of prodromal mutation carriers (n=29) and noncarriers (n=34) of HD (Larsson et al., 2008).

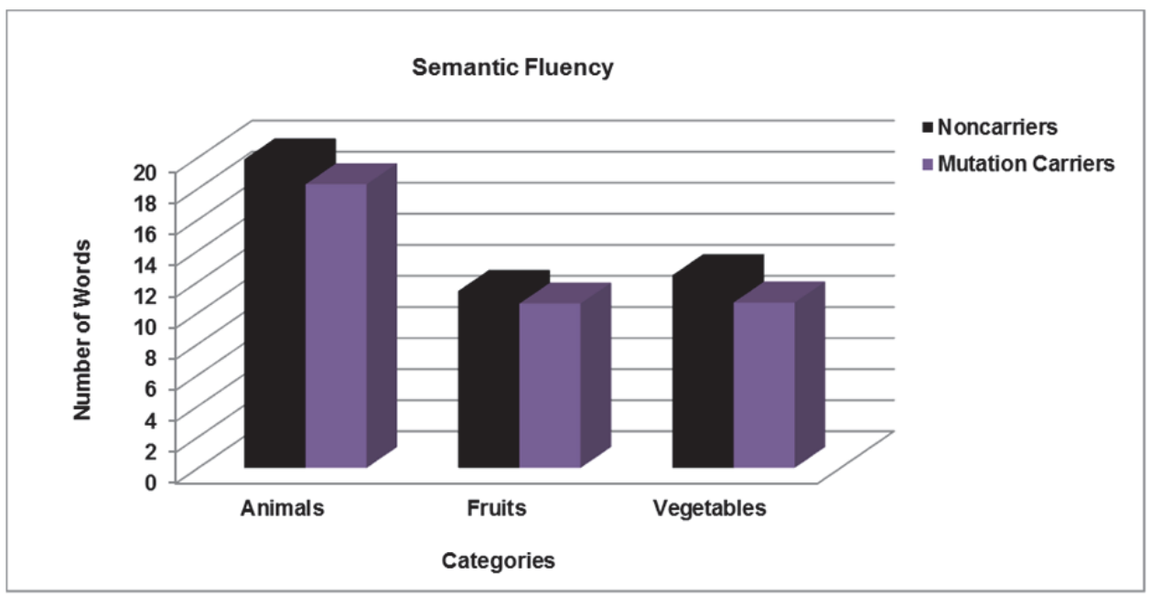

Fig. 6. Semantic fluency as measured by the categories Animals, Fruits and Vegetables in a Swedish sample of prodromal mutation carriers (n=29) and noncarriers (n=34) of HD (Larsson et al., 2008).

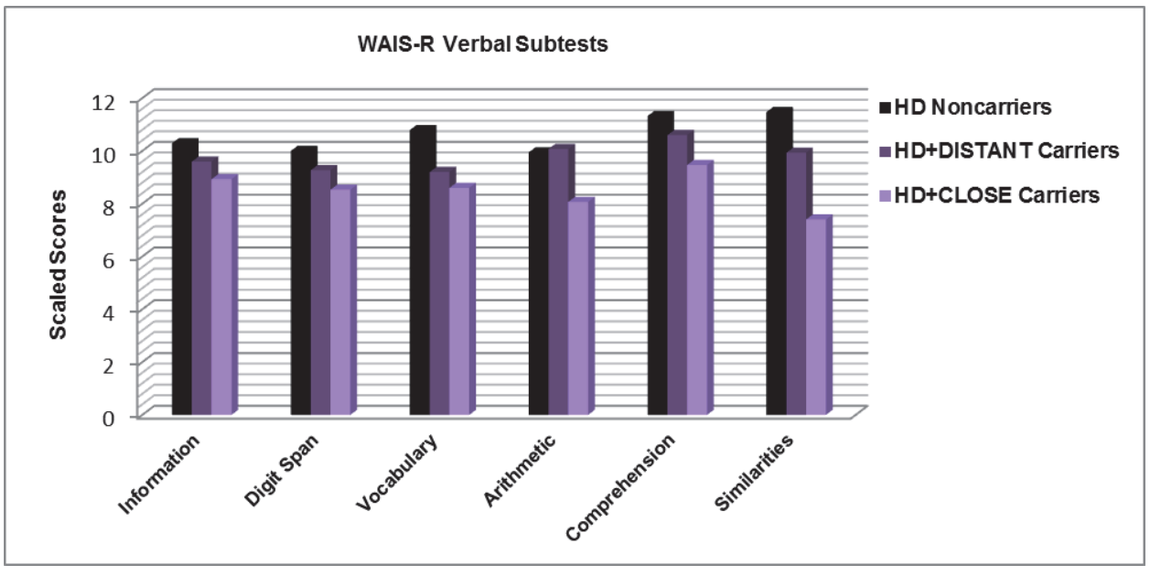

Fig. 7. Weighted scores in the WAIS-R Verbal subtests in noncarriers (HD noncarriers, n=35), mutation carriers with 12 or more years to disease onset (HD DISTANT onset, n=15) and mutation carriers with less than 12 years to disease onset (HD CLOSE onset, n=15) for Huntington's Disease (Robins Wahlin et al., 2010).

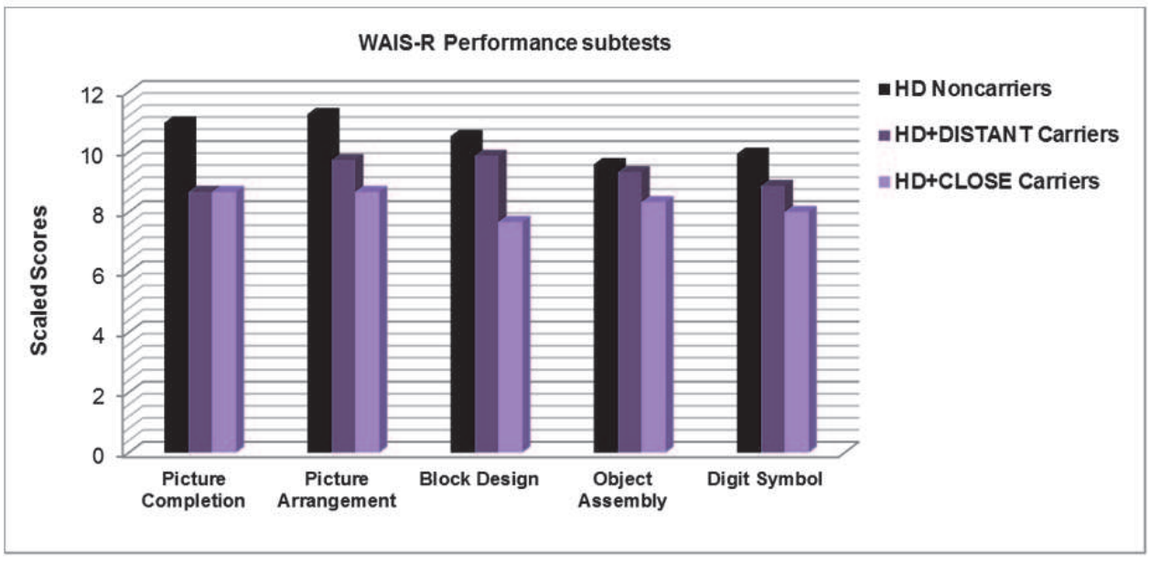

Fig. 8. Weighted scores in the WAIS-R Performance subtests in noncarriers (HD noncarriers, n=35), mutation carriers with 12 or more years to disease onset (HD DISTANT onset, n=15) and mutation carriers with less than 12 years to disease onset (HD CLOSE onset, n=15) for Huntington's Disease (Robins Wahlin et al., 2010).

7.3 Comprehensive psychometrics

Neuropsychological testing is recommended every two years to identify early signs of cognitive disabilities in mutation carriers, with the test battery covering a wide range of cognitive functions. *Verbal fluency* must always be included and it is worth noting that *phonemic fluency* shows earlier reductions than *semantic fluency* (Larsson et al., 2008). This pattern indicates that the frontal functions are involved at an early stage in disease progress. The most common categories of semantic fluency are animals, professions, vegetables and means of transport, for which there are normative data (Strauss et al., 2006). Numerous tests are available to test *Episodic Memory* with both verbal (words, sentences) and non-verbal materials (faces, objects, spatial positions and geometric shapes) (Lezak et al., 2004; Strauss et al., 2006). Furthermore, both free recall and recognition tests can be administered directly after the learning opportunity and also after longer time intervals (Lezak et al., 2004). Tests of Vocabulary and Information (WAIS, Figure 7) are useful to study *Semantic memory* (Wechsler, 1997). *Short-term memory* can be examined in both verbal (Digit Span, see Figure 7) and non-verbal (Corsi Block) tasks, while *procedural memory* can be studied with the Tower of London or Tower of Hanoi test (Figure 2). Appropriate tests for *executive functions* and *psychomotor speed* are the Stroop and the TMT A & B. The Wisconsin Card Sorting Test is less appropriate because it is time-consuming and has been shown to be not sensitive to HD (Grant & Berg, 1948; Milner, 1963). Block Design (WAIS, Figure 8), the Rey-Osterrieth Complex Figure test (ROCF, Figure 3 and 4) (Osterrieth, 1944; Rey, 1941)] and Mental Rotations (Vanderberg, 1971) are sensitive for *visuospatial features* (Robins Wahlin et al., 2007). *Mental tempo* is best noted during the neuropsychological investigations. Digit Symbol (WAIS, Figure 8) and Dots (Ekberg & Hane, 1984) or equivalent, are particularly straightforward to administer and provide reliable measures of psychomotor slowing in HD.

8. Genetic testing

8.1 Guidelines for genetic testing

The disclosure of the huntingtin gene mutation and trinucleotide CAG repeats in HD has provided new opportunities to determine diagnosis prior to the onset of motor symptoms. At risk persons may choose to find out whether they have inherited the mutation for the disease. International guidelines for genetic testing are (a) 18 years or older, (b) 50% risk of HD, (c) 25% risk of HD if parent is deceased or if the parent with a 50% risk is participating in the genetic test process (Broholm et al., 1994; Nance et al., 2003; World Federation of Neurology: Research Committee. Research Group on Huntington's chorea, 1989). The most common reasons for genetic testing are to obtain certainty for genetic status (77%), general planning for the future and family (38%), or in the interests of the children (Robins Wahlin et al., 2000). Information about genetic testing for HD is given in the clinical genetics department (or equivalent) in larger hospitals or specialized centers for HD. Prenatal diagnosis can be provided when the parents are considering termination of the pregnancy if the result shows that the fetus carries the mutation (Decruyenaere et al., 2007; Simpson & Harper, 2001). In some countries prenatal diagnosis, including IVF, is covered by public health insurance. However, approximately 35% of couples decide not to have children after undertaking genetic testing (Decruyenaere et al., 2007). In practice, however, only a small minority of at risk individuals elects to undergo genetic testing for HD (Harper et al., 2000; Robins Wahlin et al., 2000).

8.2 Imaging studies in HD and prodromal HD

Neuroimaging studies such as MRI, CT, SPECT and PET provide extra support for prodromal and manifest diagnosis of HD and are also valuable tools for studying disease progression (Antonini et al., 1996; Aylward, 2007; Montoya et al., 2006b; Paulsen, 2010; Paulsen et al., 2004). Volume of basal ganglia structures is reduced long before neuropsychological deficiencies can be demonstrated (Aylward et al., 1994). Recent MRI studies indicate that atrophy begins in the caudate nucleus approximately 11 years before clinical disease debut (Aylward et al., 2004). The putamen atrophies 9 years before manifest HD, followed by the cortico-striato-thalamocortical network and the frontal lobes which are affected later in the disease process (Paulsen, 2010).

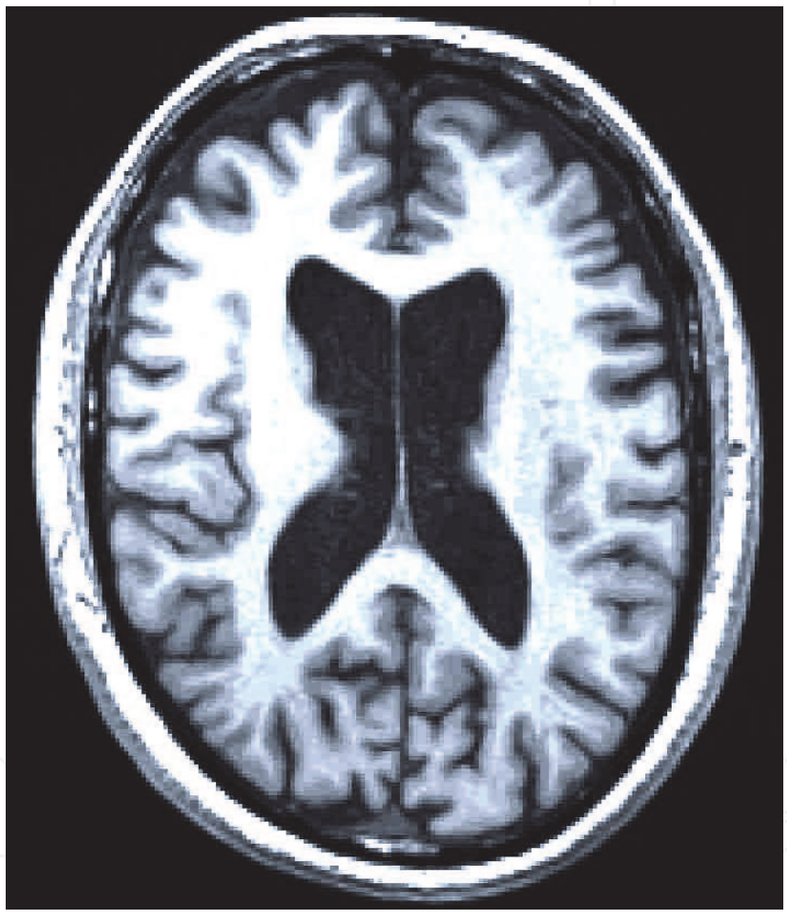

Fig. 9. MRI scan showing atrophy of the brain in Huntington's Disease (courtesy of Joakim Tedroff and Mouna Esmaeilzadeh).

Volumetric MRI data also demonstrate associations with cognitive impairments. The volume of the caudate nucleus and putamen has a strong relationship with decline in executive functions. Cortical matter degenerates later (Paulsen, 2010). PET studies have shown that other factors that contribute to cognitive impairments in HD are reduced dopamine transporter (DAT) and dopamine receptor density (D_1 and D_2) in the caudate and the putamen due to cell death (Antonini et al., 1998; Bäckman et al., 1997; Feigin et al., 2007).

A functional MRI study has shown reduced blood-oxygen-level dependent (BOLD) activity in the left dorsolateral prefrontal cortex in preclinical HD mutation carriers (Wolf et al., 2011).

8.3 Diagnostic significance

Genetic testing in recent years has provided possibilities for early diagnosis of HD and it is assumed that as the testing becomes more widely available more at risk persons will seek this information (Harper et al., 2000). There is, however, minimal research into the impact of early diagnosis on persons who are at risk of developing HD (Robins Wahlin, 2007). Some of those undergoing genetic testing will already have mild cognitive impairment that might interfere with their ability to process the results of testing. More importantly, support services are still inadequate for people who learn early in adulthood that they will develop the disease 10-40 years later. Mutation carriers and family are very concerned about cognitive impairments and dementia, since symptoms in HD are multifaceted and it is difficult to specify exactly how cognitive decline will begin. The provision of factual information to mutation carriers and family might greatly reduce fear and anxiety. This information can be provided as feedback and support in the context of neuropsychological testing or during early visits to neurologists. Effective information about the cognitive deficits in the disease and a better understanding of the long prodromal phase and time course of HD would be beneficial for affected persons and family. Counseling and support may offer opportunities for the development of psychological compensation strategies (Robins Wahlin et al., 2010; Walsh, 1999). Evaluation of therapeutic interventions in HD requires a detailed neurological/neuropsychological examination based on cognitive and clinical methods. Blood workup is indicated to exclude other diseases affecting cognitive and everyday functions.

9. Therapy and approach

9.1 Treatment and care

There are currently no effective, disease-modifying treatments for HD that might prevent its onset or slow down its progress (Mestre et al., 2009a, 2009b). In addition, the cognitive deficits found in HD are not susceptible to treatment. However, early detection of HD offers the potential in the future for prodromal diagnosis and early use of medication thereby possibly modifying its course. Treatment with donepezil (a cholinesterase inhibitor used primarily for symptomatic treatment in Alzheimer's disease) has not been shown to improve motor performance or cognition in HD. Recent studies of treatment with an omega-3 fatty acid (ethyl-eicosapentaenoic acid) and vitamin E did not show any beneficial effects (Feigin et al., 1996; Mestre et al., 2009a). However, the anti-dopaminergic, monoamine depleting agent, tetrabenazine, has been shown to be effective for the treatment of involuntary movements, but not for cognitive impairment or depression (Mestre et al., 2009b). Symptomatic treatment with small doses of conventional neuroleptics (eg haloperidol) and atypical neuroleptics (eg olanzapine), can be used to treat psychotic symptoms and outbursts of aggression (Grove et al., 2000; Warby et al., 2007). Valproic acid has been used to treat myoclonic hyperkinesia and anti-parkinsonian medication can improve hypokinesis and rigidity. However, medication containing L-dopa can also increase the severity of choreatic movements. Benzodiazepines can reduce irritability and aggressiveness, as well as help with anxiety and sleep disorders. Neuropsychiatric problems

are treated in the usual way in the early stages of HD and such treatment can be of great benefit to the patient and the family in crisis. If the patient has delusions or hallucinations, contact with a psychiatrist is desirable, since treatment with neuroleptics is often complex. Side effects of neuroleptics may be unfavorable for the patient's cognition and this needs to be balanced in treatment. Depression should always be treated with medication and if possible with psychological therapy (such as cognitive behavior therapy) or regular clinical contact. Antiepileptic treatment is sometimes indicated, especially in juvenile HD.

9.2 Clinical relevance and the approach to cognitive handicap

Cognitive impairments in the prodromal phase of HD often reduce the working lives of mutation carriers and may even lead to major crises. The inertia, reduced psychomotor speed and cognitive decline, especially affecting attention and visuospatial cognition (Lawrence et al., 2000), may lead to issues with driving ability, thus causing social and mobility problems (Beglinger et al., 2010). A formal on-road driving assessment may be needed for those individuals with preclinical or clinical HD who dispute the clinician's assessment of their likely driving ability. Through a thorough explanation of any cognitive disabilities, patients can understand and learn to adapt to the signs of approaching HD and to some extent compensate for the lost abilities. The development of the disease and cognitive disabilities requires annual follow-up as a minimum and compassionate measures in explaining, communicating and organizing supportive interventions, thus providing higher quality of life for struggling HD patients and families (Robins Wahlin et al., 1997).

9.3 Specific approach for the mutation testing

Choosing to have oneself tested should always be an individual choice and a thorough psychosocial evaluation should precede any such testing (Copley et al., 1995). A genetic test should never be imposed on an individual from any direction, especially as genetic discrimination against HD persons has been noted, although fortunately it is rare (Harper et al., 2004; Robins Wahlin, 2007). From 1993 onwards, direct mutation analysis has been used in most developed countries. This has allowed precise determination of an individual's mutation status (Huntington's Disease Collaborative Research Group, 1993). Prenatal diagnosis is available as well as prenatal exclusion testing if the prospective parents do not wish to know their genetic status (Warby et al., 2007). In some countries, as for instance in Belgium, prenatal exclusion testing using linkage analysis, pre-implantation genetic diagnosis exclusion testing and non-disclosure is available for at risk persons who want to exclude the mutation in their offspring but do not want to know their own carrier status (Decruyenaere et al., 2007). International consensus argues that children and young people under 18 years of age should not be tested for the HD mutation (Warby et al., 2007; 1989). Testing of minors is not ethically defensible because it removes the individual's option to know or not know and may cause stigma within the family and society (Robins Wahlin, 2007). It may also have serious educational and career consequences.

9.4 Psychological support during genetic testing

Since there is currently only limited symptomatic relief available, it is important for genetic counseling to occur both before and after disclosure of the results of genetic testing (Hedera, 2001). Many patients feel ambivalent about knowing their risk status (Robins Wahlin, 2007).

The request is often for an immediate and quick investigation but frequently the at risk person does not attend the appointment, only to request a new one later. Changing the at risk status to mutation carrier or noncarrier status is a psychologically complex process, which should not be rushed. The candidate's defence mechanisms and history of stress tolerance are key variables in this difficult process. After the discovery of their genetic status all candidates experience an immediate period of adaptation (Robins Wahlin, 2007). Many mutation carriers undergo a process of denial and a long period of significantly increased stress and depression, leading to long-term sick leave (Paulsen et al., 2010). Sometimes even those who find out that they do not carry the mutation have great difficulty adapting to their new genetic status, which may show itself in survivor guilt and even require therapy or counseling (Robins Wahlin et al., 1997). Psychosomatic symptoms of stress, anxiety and depression generally require symptomatic treatment and a therapy contact can be envisaged (Robins Wahlin et al., 2000).

9.5 Support actions

Personality changes and odd behavior associated with HD may also lead to relationship difficulties within the family (Close Kirkwood et al., 2002b). Catastrophic reactions to the cognitive impairment that is integral to HD and other psychosocial crises require professional support for the whole family (Robins Wahlin, 2007). Psychological support is critical when HD is complicated by depression and suicidal thoughts (Paulsen et al., 2005b; Robins Wahlin et al., 2000). Since HD has major consequences for the entire family, the therapeutic team needs to look beyond the individual patient. Psychological and social care planning can be adapted according to the different phases of illness seen in HD (Walker, 2007). Different stages require varying degrees of assistance from psychiatrists, neurologists, social workers, guardians, dietitians, speech therapists, dental hygienists, physiotherapists, occupational therapists or clinical psychologists (Paulsen et al., 2005a). In the later stages of the illness, the HD patient often has difficulty eating, swallowing and managing their personal hygiene. Incontinence and balance problems make the patient dependent on total care (Warby et al., 2007; World Federation of Neurology: Research Committee. Research Group on Huntington's chorea, 1989). Management of basic ADL functions requires a personal carer in the affected family or nursing home, as the ADL management becomes increasingly important in the late HD stages. As family members witness severe cognitive decline in the affected person, their own predisposition to the mutation constitutes an additional strain. Siblings, children and grandchildren often becomes isolated from the rest of society and need additional support (Dewhurst et al., 1970).

9.6 Diagnostic significance and cognitive testing

Genetic testing for HD has in recent years provided opportunities for early diagnosis and evidence to date suggests that demand for genetic testing will increase in the future. However, knowledge is still inadequate about the psychological and physical impact of early diagnostics on people who are at risk of HD and those who learn that they will develop the disease. Family members and mutation carriers are often concerned about cognitive impairments and dementia. As the signs and symptoms in HD are multifaceted and clinicians cannot specify how and when the early indications will show, provision of factual information to carrier and family will greatly reduce fear and anxiety. This

information to the patient can be provided by means of feedback and support in the context of neuropsychological testing by a psychologist or during medical visits. Diagnostic information about the symptomatic and cognitive profile provides the best understanding of the disease to the carrier and family. To evaluate therapeutic interventions requires a detailed neurological/neuropsychological examination based on cognitive, clinical and sometimes even experimental methods. Significant progress in understanding cognition in prodromal HD has reinforced the need for HD to be viewed as both a cognitive and motor disease. Cognition needs to be viewed as a component of quality of life and this recognition by clinicians will aid in the treatment of the long prodromal stages of the disease.

9.7 Future directions

HD is an uncommon but devastating condition for which there is currently no effective disease-modifying treatment. Symptomatic treatments are only modestly effective for some manifestations of the illness. Subtle cognitive impairment commences well before motor manifestations in many patients, complicating social and occupational functioning. Dementia is inevitable if the person with HD lives long enough. Because of the autosomal dominant pattern of HD inheritance, the ability to definitively identify mutation carriers and the availability of mouse models with various phenotypes, the future of HD research should be positive. Clinical trials of putative disease-modifying treatments in preclinical HD mutation carriers are needed. Such trials will need to assess HD carriers serially with both neuropsychological and neuroimaging tests, as well as other more specific biomarkers (Weir et al., 2011). Public and philanthropic funds will be needed for the development of therapies for HD as its low-prevalence status is unlikely to drive sufficient entrepreneurial interest. However, further research into the slowly progressive cognitive impairment found in people with HD might serve as a useful model for other neurodegenerative conditions with less certain etiological factors.

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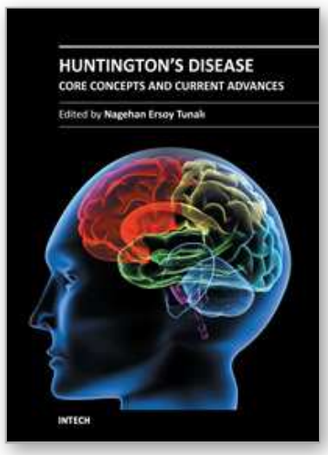

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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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