The UHDRS and UHDRS-FAP assessments in Huntington's disease

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CHAPTER 1

Introduction

Huntington's disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by motor disturbances, cognitive decline, psychiatric symptoms, and functional disability. It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene on chromosome 4.[1] A CAG expansion of 36 repeats or more is associated with HD, although only a CAG repeat length of 40 or more is considered fully penetrant and will cause HD inevitably.[2] The mean age of disease onset is 30-50 years, with a mean disease duration of 17-20 years.[3] Age of onset is inversely correlated to CAG repeat length.[4,5] Brain atrophy is most pronounced in the caudate nucleus and putamen of the striatum.[6] Atrophy is already detectable before disease onset and progresses throughout the course of the disease.[7]

HD is a rare disorder with a prevalence of 5-10 per 100,000 in the Caucasian population.[3] In the Netherlands, the total number of HD patients is approximately 1,700. About 6,000 to 9,000 people are at risk for developing HD. Genetic testing is available for individuals at risk. This test can identify premanifest gene carriers, who do not show symptoms or signs of HD yet, but will develop HD in the future. After disease onset, patients are referred to as manifest. Severity of HD progresses from early stage HD to late stage HD over time.[8]

Clinical features

HD is clinically characterized by a triad of motor, cognitive, and behavioral symptoms. The most distinctive motor symptom of HD is chorea; involuntary, irregular movements of the face, trunk, and limbs. Other motor symptoms include bradykinesia, dystonia, impairment of oculomotor function, and gait/balance problems. As the disease progresses, chorea tend to decline, while dystonia, bradykinesia, dysarthria and dysphagia become more prominent.[3,9] Cognitive decline is another sign of HD. Typically, impairment in executive functioning, memory, and psychomotor speed arise in HD.[10] The third main clinical feature of HD is behavioral change. Frequently reported psychiatric symptoms are depression, anxiety, irritability, and apathy.[11] Depression and anxiety are common in the mild-to-moderate disease severity stages, while apathy is especially prevalent in more advanced severity stages.[12-15]

HD is presently incurable and it is not possible to delay either onset or progression of the disease. Due to the progressive nature of the disease, the clinical features ultimately lead to functional decline and loss of independency. As a result, it becomes more difficult for care to be provided at home, which may lead to nursing home admission.

Assessment scales

Multiple rating scales and instruments to detect and monitor the severity and progression of clinical features in HD have been developed over the years. Some assessment scales, such as the Unified Huntington's Disease Rating Scale (UHDRS) and the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP), have a categorical and semi-quantitative design.[16,17] Other measurement instruments, such as eye-tracking equipment, tongue force analysis, and quantitative-motor (Q-Motor) assessments, have a continuous, quantitative, and more objective design.[18-20]

The clinical assessment of symptoms and signs in HD is usually performed with the UHDRS, developed by the Huntington Study Group (HSG).[16] The UHDRS is divided into four domains: motor performance, cognitive function, behavioral abnormalities, and functional abilities. The motor section assesses chorea, dystonia, eye movements, bradykinesia/rigidity, and gait/balance. Cognitive function is measured by the Verbal Fluency test, the Symbol Digit Modalities test, and the Stroop test (color naming, word reading, and interference).[21-23] The behavioral domain comprises depression, anxiety, irritability/aggression, obsessive-compulsive behaviors, psychosis, and apathy. Functional ability is assessed by the Total Functional Capacity (TFC), the Functional Assessment Scale (FAS), and the Independence Scale (IS). The UHDRS has been developed to follow individual patients systematically over time, and monitor disease progression for both research purposes and for use in clinical practice. The motor, cognitive, and functional domains of the UHDRS have demonstrated to be sensitive to detect longitudinal changes in manifest HD patients.[16,24-28]

In late stage HD, ceiling and floor effects of the UHDRS hamper the detection of changes and, therefore, disease progression is difficult to measure in patients with advanced HD.[28,29] For this reason, the UHDRS-FAP has been developed.[17] This scale consists of four sections, which are a motor, cognitive, somatic, and behavioral section. The items of the domains are adjusted for more severely affected patients.

This thesis

The main aim of this thesis was to investigate different measurement properties of the UHDRS and UHDRS-FAP in various severity stages of HD. The UHDRS is widely used in therapeutic clinical trials in HD and the motor domain, which is also called the Total Motor Score (TMS), often serves as primary endpoint to assess efficacy of interventions. Therefore, a high interrater reliability is desirable to determine the course of the motor

symptoms over time. A teaching video has been developed by the European Huntington's Disease Network (EHDN), in collaboration with the HSG, and an annual online certification has been implemented for this purpose in 2009.[30] In **chapter 2**, we aimed to investigate the interrater reliability of the UHDRS-TMS and of its subitems, using the ratings of the online certification. We also examined the impact of the annual certification on rater performance. In **chapter 3**, we focus on the oculomotor items of the UHDRS-TMS. The aim was to find out which of these items were affected in premanifest gene carriers compared to healthy controls and might be useful for detecting early clinical signs of HD.

In advanced stages of HD, knowledge is limited about the course of the clinical manifestations. Hardly any information on sensitive disease outcome measures to track disease progression is available and guidelines for management and care in long-term care facilities are limited.[31] Therefore, we aimed to explore the properties of the UHDRS-FAP and UHDRS in patients with advanced HD residing in a nursing home or receiving day-care. We investigated the capacity of the scales to differentiate between patients in the later stages of the disease using our cross-sectional data (**chapter 4**). Internal consistency and interrater reliability of both scales are also reported. The rating scales were administered again after six months. With our longitudinal data, we examined if the UHDRS-FAP and UHDRS could detect disease progression in patients with late stage HD (**chapter 5**). In **chapter 6**, we aimed to identify predictors for institutionalization by examining differences between nursing home residents and day-care patients with HD. Identification of predictors may lead to interventions and treatment strategies that can postpone the need for nursing home admission. In the final chapter (**chapter 7**), we discuss our conclusions and make recommendations for future research.

References

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

2. Rubinsztein DC, Leggo J, Coles R, Almqvist E, Biancalana V, Cassiman J-J, et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. Am J Hum Genet 1996; 59: 16–22.

3. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

4. Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 1993; 4: 387–392.

5. Stine OC, Pleasant N, Franz ML, Abbott MH, Folsteln SE, Ross CA. Correlation between the onset age of Huntington's disease and length of the trinucleotide repeat in IT-15. Hum Mol Genet 1993; 2: 1547–1549.

6. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 1985; 44:559–577.

7. Aylward EH, Sparks BF, Field KM, Yallapragada V, Shpritz BD, Rosenblatt A, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. Neurology 2004; 63: 66–72.

8. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

9. Novak MJU, Tabrizi SJ. Huntington's disease. BMJ 2010; 340: c3109.

10. Dumas EM, Van den Bogaard SJA, Middelkoop HAM, Roos RAC. A review of cognition in Huntington's disease. Front Biosci 2013; 5: 1–18.

11. Van Duijn E, Kingma EM, Van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci 2007; 19: 441–448.

12. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci 2012; 24: 53–60.

13. Paulsen JS, Nehl C, Ferneyhough Hoth K, Kanz JE, Benjamin M, Conybeare R, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci 2005; 17: 496–502.

14. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 219–226.

15. Kingma EM, Van Duijn E, Timman R, Van der Mast RC, Roos RAC. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008; 30: 155–161.

16. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

17. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

18. Blekher TM, Yee RD, Kirkwood SC, Hake AM, Stout JC, Weaver MR, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. Vision Res 2004; 44: 2729–2736.

19. Reilmann R, Bohlen S, Klopstock T, Bender A, Weindl A, Saemann P, et al. Tongue force analysis assesses motor phenotype in premanifest and symptomatic Huntington's disease. Mov Disord 2010; 25: 2195–2202.

20. Reilmann R, Bohlen S, Kirsten F, Ringelstein EB, Lange HW. Assessment of involuntary choreatic movements in Huntington's disease – Toward objective and quantitative measures. Mov Disord 2011; 26: 2267–2273.

21. Benton AL, Hamsher K DeS. Multilingual aphasia examination manual. Iowa City: Univ Iowa, 1978.

22. Smith A. Symbol digit modalities test manual. Los Angeles: West Psychol Serv, 1973.

23. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643–662.

24. Siesling S, Van Vugt JPP, Zwinderman KAH, Kieburtz K, Roos RAC. Unified Huntington's Disease Rating Scale: a follow up. Mov Disord 1998; 13: 915–919.

25. Meyer C, Landwehrmeyer B, Schwenke C, Doble A, Orth M, Ludolph AC. Rate of change in early Huntington's disease: a clinicometric analysis. Mov Disord 2012; 27: 118–124.

26. Toh EA, MacAskill MR, Dalrymple-Alford JC, Myall DJ, Livingston L, Macleod SAD, et al. Comparison of cognitive and UHDRS measures in monitoring disease progression in Huntington's disease: a 12-month longitudinal study. Transl Neurodegener 2014; 3: 15.

27. Feigin A, Kieburtz K, Bordwell K, Como P, Steinberg K, Sotack J, et al. Functional decline in Huntington's disease. Mov Disord 1995; 10: 211–214.

28. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

29. Baake V, Reijntjes RHAM, Dumas EM, Thompson JC, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017; 95: 51–62.

30. Reilmann R, Roos R, Rosser A, Grimbergen Y, Kraus P, Craufurd D, et al. A teaching film, video library and online certification for the Unified Huntington's Disease Rating Scale Total Motor Score. Akt Neurol 2009; 36: 474.

31. Simpson SA. Late stage care in Huntington's disease. Brain Res Bull 2007; 72: 179–181.

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CHAPTER 2

Interrater reliability of the Unified Huntington's Disease Rating Scale-Total Motor Score certification

Abstract

Background: The clinical assessment of motor symptoms in Huntington's disease is usually performed with the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). A high interrater reliability is desirable to monitor symptom progression. Therefore, a teaching video and a system for annual online certification has been developed and implemented.

Objectives: The aim of this study is to investigate the interrater reliability of the UHDRS-TMS and of its subitems, and to examine the performance of raters in consecutive years.

Methods: Data from the online UHDRS-TMS certification were used. The interrater reliability was assessed for all first-time participants (n = 944) between 2009 and 2016. Intraclass correlation coefficients (ICC) were calculated for each year separately and the mean was taken as the total ICC.

Results: The UHDRS-TMS (ICC = 0.847), tandem walking (0.824), pronate/supinate hands left (0.713), and retropulsion pull test (0.706) showed good interrater reliability. Poor interrater reliability was found for maximal dystonia of the left and right upper extremity (0.187 and 0.322, respectively), maximal dystonia of the left and right lower extremity (0.200 and 0.256, respectively), and maximal dystonia of the trunk (0.389), tongue protrusion (0.266), and rigidity arms left (0.390). Raters performed significantly worse on follow-up certification compared to their first certification.

Conclusions: Our results suggest that the rating of dystonia (absent, slight, mild, moderate, or marked) is subjective and difficult to interpret, especially on video. Therefore, changing the dystonia items of the UHDRS-TMS should be explored. We also recommend that raters should watch the UHDRS-TMS teaching video before each certification.

Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by motor disturbances, cognitive decline, psychiatric symptoms and functional disability.[1] It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion on chromosome 4 in the Huntingtin gene.[2] The mean age at disease onset is between 30 and 50 years.[3]

The clinical assessment of symptoms and signs in HD is usually performed with the Unified Huntington's Disease Rating Scale (UHDRS), developed by the Huntington Study Group (HSG).[4] The UHDRS assesses four domains: motor function, cognitive function, behavioral abnormalities, and functional capacity. It was developed to follow individual patients systematically over time and monitor disease progression for both research purposes and for use in clinical practice. The sensitivity of the scale to detect longitudinal changes has been demonstrated by observational studies in manifest HD patients. In particular, the Total Motor Score (TMS) and the Total Functional Capacity (TFC) have been shown to deteriorate significantly during one-year follow-up.[4-9]

The UHDRS is widely used in therapeutic clinical trials in HD and the UHDRS-TMS often serves as primary endpoint to assess efficacy of interventions. Therefore, a high interrater reliability is desirable to determine the course of the motor symptoms over time. Available data suggest that the interrater reliability of the TMS is high, with an intraclass correlation coefficient of 0.94.[4]

In order to establish a high interrater reliability of the UHDRS-TMS, the European Huntington's Disease Network (EHDN), in collaboration with the HSG, developed a teaching video for the UHDRS-TMS and established an annual online system of UHDRS-TMS certification.[10,11] Despite this effort, we hypothesize that several items of the TMS are highly subjective and difficult to score. We therefore aim to investigate the interrater reliability of the UHDRS-TMS and of its subitems in the large database of ratings performed for annual online certification. We also aim to examine the impact of annual certification on rater performance to assess if certification increases accuracy over time.

Methods

Certification, which only involves the motor section of the UHDRS (not the cognitive, behavioral and functional domains) is mandatory for all individuals who carry out the motor section of the UHDRS in clinical trials. The UHDRS-TMS consists of 31 items (Table 1), with varying response options ranging from zero (normal/not affected) to four (cannot

perform/severely affected; see Supplement 1 for all response options per item). Hence, the total range of the UHDRS-TMS is 0 to 124. Higher scores generally indicate more severe motor impairment. Data from the annual UHDRS-TMS online certification were used for this study. The procedure consists of assessing three videos of patients with HD and providing the UHDRS-TMS ratings. In order to pass certification, it is necessary to rate at least two of the three videos correctly, which means 24 out of the 31 items must be rated correctly, the range of acceptable answers being defined by a panel of EHDN and HSG experts. If a rater fails, he is given the chance to rate a new set of three videos, but if he fails again, he will not be certified to perform the UHDRS-TMS and will be referred for further expert training.

UHDRS-TMS certification started in 2009.[10] The present study includes the first attempt of each rater in each year between 2009 and 2016. In 2012, biannual certification was proposed and implemented, but was soon reversed, with annual certification resuming in 2014. Therefore, the raters who participated in 2012 did not have to perform the certification in 2013, and the raters who participated in 2013 scored the same three videos as the raters who participated in 2012.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 23. The interrater reliability of the UHDRS-TMS and its subitems was assessed for all first attempts with the intraclass correlation coefficient (ICC). We used a two-way random model with absolute agreement. ICC values were calculated for each year separately and the mean of this ICC was taken as the total ICC. An ICC higher than 0.7 was defined as good; a value lower than 0.4 was considered poor.[12,13] The percentage of raters who scored the separate motor items of the UHDRS correctly was determined using all first efforts. This was compared to the range of acceptable answers defined by the panel of HD experts. Follow-up performance was based on the results of raters who had carried out at least one rating, one year after their first participation. Because videos in consecutive years might differ in difficulty, we also assessed the follow-up of raters who participated for the first time in 2010 and again in 2012, years in which the same three videos were used. The raters were not informed about the use of the same videos. The percentage of UHDRS motor items rated correctly was calculated per certification, and compared using a paired sample t-test. A p-value of <0.05 was considered statistically significant.

Results

The total number of examinations performed between 2009 and 2016 was 1,982 and the number of first participations was 944, therefore many raters participated multiple times. The majority of raters in this study were physicians with different levels of expertise; however, nurses and other health care professionals also took part. The interrater reliability of the UHDRS-TMS, the separate subitems, and the total dystonia and chorea scores is shown in Table 1. The mean UHDRS-TMS of all videos was 31.9 (range 0 to 82). ICC values were high for the TMS (0.847), tandem walking (0.824), pronate/supinate hands left (0.713), and retropulsion pull test (0.706). Low ICC values were found for maximal dystonia of the left and right upper extremity (LUE and RUE; 0.187 and 0.322, respectively), maximal dystonia of the left and right lower extremity (LLE and RLE; 0.200 and 0.256, respectively), maximal dystonia of the trunk (0.389), tongue protrusion (0.266), and rigidity arms left (0.390).

For every subitem of the UHDRS-TMS, we calculated the percentage of raters who rated the item within the accepted range at their first participation (Table 1). Often, the expert panel defined more than one answer as correct, and therefore the mean number of options defined as correct is also reported. Gait (95.8%), retropulsion pull test (95.2%), dysarthria (94.1%), finger taps left (93.0%), and maximal chorea of the trunk (90.5%) were the items that were most often rated correctly. Saccade velocity vertical (76.5%), saccade velocity horizontal (76.8%), maximal chorea LUE (76.8%), luria (77.4%), and maximal chorea RUE (78.5%) were more difficult to score.

Table 1. Interrater reliability for all UHDRS-TMS items at first participation (n = 944)

	ICC with 95% CI	Percentage of raters who scored the item correctly	Mean number of options defined as correct
1. Ocular pursuit horizontal	0.623 (0.509-0.737)	83.9%	2.0
2. Ocular pursuit vertical	0.662 (0.591-0.732)	84.7%	2.1
3. Saccade initiation horizontal	0.592 (0.462-0.721)	83.7%	2.1
4. Saccade initiation vertical	0.610 (0.413-0.807)	84.5%	2.0
5. Saccade velocity horizontal	0.591 (0.431-0.751)	76.8%	2.0
6. Saccade velocity vertical	0.564 (0.438-0.689)	76.5%	2.3
7. Dysarthria	0.452 (0.208-0.695)	94.1%	1.6

8. Tongue protrusion	0.266 (-0.031-0.562)	83.5%	1.2
9. Finger taps right	0.413 (0.114-0.711)	84.3%	1.7
10. Finger taps left	0.569 (0.310-0.828)	93.0%	1.9
11. Pronate/supinate hands right	0.598 (0.375-0.821)	88.8%	1.5
12. Pronate/supinate hands left	0.713 (0.547-0.879)	88.9%	1.7
13. Luria	0.478 (0.188-0.768)	77.4%	1.3
14. Rigidity arms right	0.598 (0.518-0.678)	89.4%	1.7
15. Rigidity arms left	0.390 (0.174-0.607)	89.2%	1.5
16. Bradykinesia body	0.588 (0.454-0.723)	87.4%	2.1
17. Maximal dystonia trunk	0.389 (0.277-0.500)	87.7%	1.9
18. Maximal dystonia RUE	0.322 (0.095-0.549)	86.7%	1.7
19. Maximal dystonia LUE	0.187 (0.058-0.316)	83.8%	1.7
20. Maximal dystonia RLE	0.256 (0.134-0.377)	83.8%	1.7
21. Maximal dystonia LLE	0.200 (0.061-0.338)	83.3%	1.7
22. Maximal chorea face	0.597 (0.516-0.677)	88.7%	2.1
23. Maximal chorea BOL	0.551 (0.415-0.687)	86.5%	2.2
24. Maximal chorea trunk	0.685 (0.541-0.829)	90.5%	2.1
25. Maximal chorea RUE	0.508 (0.359-0.657)	78.5%	1.9
26. Maximal chorea LUE	0.446 (0.213-0.679)	76.8%	1.9
27. Maximal chorea RLE	0.572 (0.447-0.696)	85.1%	2.1
28. Maximal chorea LLE	0.615 (0.499-0.732)	89.6%	2.1
29. Gait	0.642 (0.421-0.864)	95.8%	1.6
30. Tandem walking	0.824 (0.693-0.955)	88.1%	1.4
31. Retropulsion pull test	0.706 (0.524-0.888)	95.2%	1.4
UHDRS-TMS	0.847 (0.766-0.928)	NA	NA
Total dystonia score	0.369 (0.182-0.555)	NA	NA
Total chorea score	0.670 (0.516-0.825)	NA	NA

ICC values were calculated using a two-way random model with absolute agreement. ICC values were calculated for each year separately and the mean of this ICC was taken as the total ICC (with 95% CI).

Abbreviations: BOL, buccal-oral-lingual; CI, confidence interval; ICC, intraclass correlation coefficient; LLE, left lower extremity; LUE, left upper extremity; NA, not applicable; RLE, right lower extremity; RUE, right upper extremity; UHDRS-TMS, Unified Huntington's Disease Rating Scale-Total Motor Score.

Table 2. Performance of raters on the UHDRS-TMS certification over time

	Percentage of UHDRS-TMS items scored correctly	*p*-value
First certification (n = 226)	86.6% (±6.3)	**0.004**
Second certification one year later (n = 226)	85.1% (±6.7)	
First certification in 2010 (n = 81)	87.8% (±5.0)	**0.045**
Same certification in 2012 (n = 81)	86.4% (±6.3)	

Data are mean (with standard deviation). *p*-values were calculated using paired sample t-tests.
Abbreviations: UHDRS-TMS, Unified Huntington's Disease Rating Scale-Total Motor Score.

The performance of raters on the UHDRS-TMS certification over time is presented in Table 2. The number with one or more follow-up participations one year after their first rating was 226. At their first examination, the raters scored 86.6% of the motor subitems correctly. One year later, at their second certification, the score dropped significantly to 85.1% (p = 0.004). Eighty-one raters participated for the first time in 2010 and saw the same three videos in 2012. The percentage of items scored correctly dropped significantly from 87.8% in 2010 to 86.4% in 2012 (p = 0.045).

Discussion

This study in a large cohort of raters showed a good interrater reliability of the UHDRS-TMS. We found an intraclass correlation coefficient of 0.847, which is lower than the ICC of 0.94, previously reported by the HSG.[4] An even higher ICC of 0.97 was found in patients with advanced HD.[14] An important difference between the previously mentioned studies and our study is that we examined patients using videos instead of performing an actual physical examination. This may have caused differences in rating certain motor items, especially rigidity. Muscle tone can only be felt when examining the patient physically and cannot be seen on a video. When examining patients using video recordings, one might expect a better interrater reliability, because the clinical presentation of the patients is standardized and does not vary. However, our study did not show this. An important explanation for the lower interrater reliability of the UHDRS-TMS in our study compared to the study by the HSG is more than likely the fact that the raters involved in our study had variable levels of experience, and were not all HD experts. However, the results of our study are probably more relevant, as raters in clinical trials are likely to be more junior. The higher ICC reported by the HSG may also be caused by the limited number of raters involved.

When we investigated the subitems of the UHDRS-TMS, we found a good interrater reliability for tandem walking, pronate/supinate hands left, and retropulsion pull test. To our knowledge no other study investigated the interrater reliability of the subitems of the UHDRS-TMS. However, the HSG did provide the ICC for the total chorea score (i.e., 0.82), and for the total dystonia score (i.e., 0.62).[4] These ICC values are also higher than the ICC values for the total chorea score and total dystonia score in our study (0.670 and 0.369, respectively). Especially, the subitems maximal dystonia LUE, maximal dystonia LLE, and maximal dystonia RLE showed poor interrater reliability in our analysis. We also found low interrater reliability for tongue protrusion. This is an unexpected result, because this item is characterized by clear cutoffs for each category, partly based on time, which is an objective measure. Perhaps the poor interrater reliability is caused by the difficulty of determining if the tongue is fully protruded or not.

Our study showed that all dystonia items of the UHDRS-TMS exhibit poor interrater reliability, suggesting that the rating of dystonia (absent, slight, mild, moderate, or marked) is rather subjective and very difficult to interpret, especially on video. Removing or changing (part of) the dystonia items or providing clearer response options should therefore be explored, especially because poor interrater reliability hampers monitoring HD progression in both individual patients and clinical trials. Siesling et al. performed a factor analysis on the UHDRS-TMS.[15] They found a Cronbach's alpha of 0.966 for the UHDRS-TMS. When they omitted all dystonia items, the value rose slightly, suggesting that the internal consistency of the UHDRS-TMS is still high without dystonia. However, the motor phenotype in HD is not homogenous and dystonia-predominant HD (in contrast to chorea-predominant HD) is present in some patients.[16] Accordingly, the dystonia items cannot be removed from the UHDRS-TMS entirely, since this would hamper the content validity of the scale. It is worth pointing out that the chorea items have the same scoring (absent, slight, mild, moderate, or marked) as the dystonia items. Nonetheless, the interrater reliability of the chorea items was better, possibly due to the fact that chorea is more common than dystonia in HD, particularly in patients in the earlier stages of HD seen regularly in out-patient clinics. Raters may therefore have more experience with different levels of severity of chorea. The ICC value of 0.62 for the total dystonia score found by the HSG demonstrated moderate interrater reliability and also suggested that dystonia is more difficult to score than chorea, as the ICC for the total chorea score was 0.82.[4] Furthermore, the UHDRS-TMS consists of five dystonia items that comprise 16% of the total motor score. Taking into account the poor interrater reliability for the dystonia items, we suggest reducing or combining the number of dystonia items. The same could be applied to the seven chorea items. Future studies are required to explore how the items can be improved.

For each motor item of the UHDRS, we calculated how many raters scored the item correctly at their first participation. Gait, retropulsion pull test, dysarthria, finger taps left, and maximal chorea of the trunk were rated best. More difficult items were saccade velocity vertical, saccade velocity horizontal, maximal chorea LUE, luria, and maximal chorea RUE. However, since the number of options defined as correct was different per subitem (due to the fact that different patients were scored in different years), the interpretation of which items are easy or more difficult to score is complicated and should be interpreted with caution. For example, only 76.5% of the raters scored saccade velocity vertical correctly. Even so, the mean number of options defined as correct by the expert panel was high for this item, namely 2.3. On the other hand, only 77.4% of the raters scored luria correctly, but the mean number of correct options for luria was low (1.3). This suggests that saccade velocity vertical is indeed a difficult item to score, but the low percentage of raters who scored luria correctly might be low due to the small number of options defined as correct.

We also assessed the performance of raters on the UHDRS-TMS certification longitudinally. The percentage of motor items scored correctly dropped significantly between the first and second certification one year later. One explanation might be that the videos used were not all of the same level of difficulty. Therefore, we also evaluated the performance of those raters who scored identical videos in 2010 and 2012, without this being announced beforehand. Interestingly, the percentage of motor items scored correctly also decreased significantly when re-rating the same patients. However, a decrease of 1.4% seems to be only marginally relevant. Apparently slight deviations in performing and rating the UHDRS-TMS developed over time. Perhaps raters watched the teaching video prior to their first certification, but not two years later. We recommend that raters should watch the teaching video before each certification to be reminded of the established standards. We also tried to examine the intrarater reliability of the subitems of the UHDRS-TMS for those who scored the same videos in 2010 and 2012. However, because of low variance between the raters, the intrarater reliability could not be calculated with meaningful values. This typically happens when the between-rater variation is relatively small compared to the within-rater variation due to a large number of different raters. As a result the ICC values turn out to be negative and not interpretable.

The strength of our study lies in the large cohort of raters who participated in the UHDRS-TMS certification. The online system allowed us to perform analyses with much higher precision and power, since the same video (i.e., standardized clinical presentation) was rated by a large number of raters, not just two or three. However, because a patient's clinical presentation usually varies, the use of video recordings is also a limitation of our study. Furthermore, some clinical signs might not be captured as easily on video compared to direct examination of an actual patient. Ideally, intrarater reliability based on

video and direct examination of the same patients should be investigated as it may identify those items that are most influenced by this. Another limitation is the fact that the ratings used to analyse the interrater reliability were not performed for this purpose, but for the purpose of obtaining a certification. Furthermore, we have already acknowledged that the clinical stage of patients shown, and thus the level of difficulty of the videos used in consecutive years, was not the same. This may have influenced the results. However, in real life, the clinical stages of HD patients also differ, which can make the UHDRS-TMS rating easier in some patients compared to others. In this study, it is important to note that our primary aim was to assess reliability, not validity. Both parameters are important for the final judgement of scales and to assess if removal of items would improve the scale.

In conclusion, our study found a good interrater reliability of the UHDRS-TMS. However, all dystonia items, together with tongue protrusion and rigidity arms left, showed poor interrater reliability. This suggests that the rating of these items is difficult to interpret, probably as a consequence of the subjective nature of the response options. Therefore, removing, changing, or combining some of the dystonia items, or providing clearer response options should be explored, as poor interrater reliability may have a serious negative impact on assessing progression of HD motor symptoms in both individual patients and clinical trials. Furthermore, the percentage of UHDRS-TMS subitems scored correctly dropped significantly between the first and follow-up certification. We, therefore, recommend that raters should watch the teaching video again before each certification.

References

1. Ross CA, Pantelyat A, Kogan J, Brandt J. Determinants of functional disability in Huntington's disease: role of cognitive and motor dysfunction. Mov Disord 2014; 29: 1351–1358.

2. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

3. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

4. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

5. Siesling S, Van Vugt JPP, Zwinderman KAH, Kieburtz K, Roos RAC. Unified Huntington's Disease Rating Scale: a follow up. Mov Disord 1998; 13: 915–919.

6. Meyer C, Landwehrmeyer B, Schwenke C, Doble A, Orth M, Ludolph AC. Rate of change in early Huntington's disease: a clinicometric analysis. Mov Disord 2012; 27: 118–124.

7. Toh EA, MacAskill MR, Dalrymple-Alford JC, Myall DJ, Livingston L, Macleod SAD, et al. Comparison of cognitive and UHDRS measures in monitoring disease progression in Huntington's disease: a 12-month longitudinal study. Transl Neurodegener 2014; 3: 15.

8. Feigin A, Kieburtz K, Bordwell K, Como P, Steinberg K, Sotack J, et al. Functional decline in Huntington's disease. Mov Disord 1995; 10: 211–214.

9. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

10. Reilmann R, Roos R, Rosser A, Grimbergen Y, Kraus P, Craufurd D, et al. A teaching film, video library and online certification for the Unified Huntington's Disease Rating Scale Total Motor Score. Akt Neurol 2009; 36: 474.

11. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. In: Feigin AS, Anderson KE, Eds. Handbook of Clinical Neurology: Huntington Disease. 2017; p209–226.

12. Nunnally JC, Bernstein IH. Psychometric Theory, 3rd edition. New York: McGraw-Hill, 1994.

13. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994; 6: 284–290.

14. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

15. Siesling S, Zwinderman AH, Van Vugt JPP, Kieburtz K, Roos RAC. A shortened version of the motor section of the Unified Huntington's Disease Rating Scale. Mov Disord 1997; 12: 229–234.

16. Louis ED, Anderson KE, Moskowitz C, Zeck Thorne D, Marder K. Dystonia-predominant adult-onset Huntington disease. Arch Neurol 2000; 57: 1326–1330.

Supplement 1. The Unified Huntington's Disease Rating Scale-Total Motor Score

1. Ocular pursuit horizontal	0 = complete (normal) 1 = jerky movement 2 = interrupted pursuit/full range 3 = incomplete range 4 = cannot pursue	2. Ocular pursuit vertical	0 = complete (normal) 1 = jerky movement 2 = interrupted pursuit/full range 3 = incomplete range 4 = cannot pursue
3. Saccade initiation horizontal	0 = normal 1 = increased latency only 2 = suppressible blinks or head movements to initiate 3 = unsuppressible head movements 4 = cannot initiate saccades	4. Saccade initiation vertical	0 = normal 1 = increased latency only 2 = suppressible blinks or head movements to initiate 3 = unsuppressible head movements 4 = cannot initiate saccades
5. Saccade velocity horizontal	0 = normal 1 = mild slowing 2 = moderate slowing 3 = severely slow, full range 4 = incomplete range	6. Saccade velocity vertical	0 = normal 1 = mild slowing 2 = moderate slowing 3 = severely slow, full range 4 = incomplete range
7. Dysarthria	0 = normal 1 = unclear, no need to repeat 2 = must repeat to be understood 3 = mostly incomprehensible 4 = anarthria	8. Tongue protrusion	0 = can hold tongue fully protruded for 10 seconds 1 = cannot keep fully protruded for 10 seconds 2 = cannot keep fully protruded for 5 seconds 3 = cannot fully protrude tongue 4 = cannot protrude tongue beyond lips
9. Finger taps right	0 = normal (≥15/5 seconds) 1 = mild slowing, reduction in amplitude (11-14/5 seconds) 2 = moderately impaired (7-10/5 seconds) 3 = severely impaired (3-6/5 seconds) 4 = can barely perform task (0-2/5 seconds)	10. Finger taps left	0 = normal (≥15/5 seconds) 1 = mild slowing, reduction in amplitude (11-14/5 seconds) 2 = moderately impaired (7-10/5 seconds) 3 = severely impaired (3-6/5 seconds) 4 = can barely perform task (0-2/5 seconds)
11. Pronate/ supinate hands right	0 = normal 1 = mild slowing and/or irregular 2 = moderate slowing and irregular 3 = severe slowing and irregular 4 = cannot perform	12. Pronate/ supinate hands left	0 = normal 1 = mild slowing and/or irregular 2 = moderate slowing and irregular 3 = severe slowing and irregular 4 = cannot perform

13. Luria	0 = ≥4 in 10 seconds, no cue 1 = <4 in 10 seconds, no cue 2 = ≥4 in 10 seconds with cues 3 = <4 in 10 seconds with cues 4 = cannot perform	14. Rigidity arms right	0 = absent 1 = slight or present only with activation 2 = mild to moderate 3 = severe, full range of motion 4 = severe with limited range
15. Rigidity arms left	0 = absent 1 = slight or present only with activation 2 = mild to moderate 3 = severe, full range of motion 4 = severe with limited range	16. Bradykinesia body	0 = absent 1 = minimally slow (?normal) 2 = mildly but clearly slow 3 = moderately slow, some hesitation 4 = markedly slow, long delays in initiation
17. Maximal dystonia trunk	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	18. Maximal dystonia RUE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged
19. Maximal dystonia LUE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	20. Maximal dystonia RLE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged
21. Maximal dystonia LLE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	22. Maximal chorea face	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged
23. Maximal chorea BOL	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	24. Maximal chorea trunk	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged
25. Maximal chorea RUE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	26. Maximal chorea LUE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged

27. Maximal chorea RLE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	28. Maximal chorea LLE	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged
29. Gait	0 = normal gait, narrow base 1 = wide base and/or slow 2 = wide base and walks with difficulty 3 = walks only with assistance 4 = cannot attempt	30. Tandem walking	0 = normal for 10 steps 1 = 1 to 3 deviations from straight line 2 = >3 deviations 3 = cannot complete 4 = cannot attempt
31. Retropulsion pull test	0 = normal 1 = recovers spontaneously 2 = would fall if not caught 3 = tends to fall spontaneously 4 = cannot stand		

Abbreviations: BOL, buccal-oral-lingual; LLE, left lower extremity; LUE, left upper extremity; RLE, right lower extremity; RUE, right upper extremity.

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CHAPTER 3

Premanifest Huntington's disease: examination of oculomotor abnormalities in clinical practice

Abstract

Introduction: Different oculomotor abnormalities have been reported to occur in premanifest Huntington's disease. The aim of this study is to investigate which oculomotor items of the Unified Huntington's Disease Rating Scale (UHDRS) are affected in premanifest individuals compared to healthy controls, and if CAG repeat length and age are correlated with oculomotor abnormalities in premanifest Huntington's disease gene carriers.

Methods: We compared baseline data of 70 premanifest individuals and 27 controls who participated in the Enroll-HD study at the Leiden University Medical Center, the Netherlands. Premanifest gene carriers were divided in individuals near to disease onset and individuals far from disease onset.

Results: Using a logistic regression model, only horizontal ocular pursuit of the six oculomotor items of the UHDRS was significantly more frequently affected in premanifest individuals close to disease onset compared to controls (p = 0.044, OR 13.100). Age was significantly higher in premanifest individuals with affected horizontal ocular pursuit (p = 0.016, OR 1.115) and with affected vertical ocular pursuit (p = 0.030, OR 1.065) compared to premanifest individuals without ocular pursuit deficits.

Conclusions: Our results suggest that horizontal ocular pursuit is the only affected oculomotor item of the UHDRS in premanifest individuals and could be used to assess early clinical signs of Huntington's disease. Saccade initiation and saccade velocity do not seem useful for detecting differences between premanifest individuals and controls.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive motor, cognitive and psychiatric symptoms. It is caused by an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat in the Huntingtin gene on chromosome 4.[1] The mean age at onset is between 30 and 50 years, with a range of 2 to 85 years.[2]

Many studies have focused on the identification of potential biomarkers in premanifest HD. The standard clinical assessment tool for HD is the Unified Huntington's Disease Rating Scale (UHDRS).[3] The PREDICT-HD study showed that premanifest individuals closer to estimated age of disease onset had worse scores in the chorea, the bradykinesia, and the oculomotor domain of the UHDRS than individuals further from estimated diagnosis.[4]

Several cross-sectional studies have shown that eye movements are impaired in an early stage of HD, often long before other symptoms become clinically relevant. These studies with eye-tracking equipment have found abnormal antisaccade and memory guided tasks, variability of latency, and error rates.[5-8] However, eye-tracking equipment is not easily accessible in a clinical setting. Instead, the oculomotor items of the UHDRS are much easier to use in clinical practice.

The aim of our study is to determine if the oculomotor items of the UHDRS show relevant abnormalities in premanifest HD. We also want to examine if a higher CAG expansion is associated with more oculomotor abnormalities in premanifest HD individuals compared to lower CAG expansions, considering CAG repeat length is inversely correlated with age of disease onset.[9,10] Additionally, we aim to examine the relationship of age on oculomotor deficits in premanifest HD individuals, since oculomotor abnormalities also occur under the influence of ageing in healthy people.[11,12]

Materials and methods

Baseline data of subjects participating in the Enroll-HD study at the Leiden University Medical Center (LUMC), the Netherlands, were included in this study. Enroll-HD is an observational, prospective, international, multi-center study without experimental treatment. The Medical Ethics Committee of the LUMC approved the study (P13.167) and written informed consent was obtained from all participants. Assessments performed in this study include the examination of motor functioning using the UHDRS-Total Motor Score (TMS). Testing conditions were uniform across all subjects, and according to the instructions of the UHDRS-TMS teaching film.[13] The oculomotor assessments were

performed before the other motor assessments. The UHDRS-TMS was performed by four different raters. The raters were not blinded to the status of the participants. The six oculomotor items of the UHDRS-TMS are horizontal and vertical ocular pursuit, horizontal and vertical saccade initiation, and horizontal and vertical saccade velocity (Table 1). They can all be rated from 0 'normal' to 4 'cannot perform'. Overall, higher scores indicate more severe motor impairment.

A total of 326 participants visited the neurology department of the LUMC for a baseline visit of Enroll-HD between October 2014 and September 2016. Manifest HD patients (n = 220) and participants with an unknown genotype (n = 9) were excluded. Seventy premanifest HD individuals and 27 controls (genotype negative individuals (n = 14), family controls (n = 12) and community controls (n = 1)) were included. Premanifest gene carriers were defined as having a total motor score of 5 or less on the UHDRS-TMS. Premanifest HD gene carriers were divided in premanifest individuals near to disease onset and premanifest individuals far from disease onset by the group median for expected years to HD onset (13.7 years). Expected years to onset was calculated for each individual using the formula described by Langbehn et al.[14], which is based on CAG repeat length and age at visit. Genotype negative individuals were potentially at risk for HD, but tested negative.

Table 1. The oculomotor items of the Unified Huntington's Disease Rating Scale

Ocular pursuit	0 = complete (normal)
(horizontal and vertical)	1 = jerky movement
	2 = interrupted pursuit/full range
	3 = incomplete range
	4 = cannot pursue
Saccade initiation	0 = normal
(horizontal and vertical)	1 = increased latency only
	2 = suppressible blinks or head movements to initiate
	3 = unsuppressible head movements
	4 = cannot initiate saccades
Saccade velocity	0 = normal
(horizontal and vertical)	1 = mild slowing
	2 = moderate slowing
	3 = severely slow, full range
	4 = incomplete range

Family controls were non-related family members of HD gene carriers (mainly husbands and wives). The community control volunteered and did not visit the neurology department before.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 23. Demographics were calculated using independent sample t-tests and Chi-square tests. A linear regression analysis of the UHDRS-TMS as a function of age was performed among controls. Comparisons between premanifest individuals and controls for the six oculomotor items were performed using a logistic regression model, adjusting for age and gender. The UHDRS total oculomotor score is the sum of the separate oculomotor items and comparisons for this score between premanifest individuals and controls were assessed using a linear regression model, controlling for age and gender. The relationships between oculomotor abnormalities and CAG repeat length and age were calculated using a logistic regression model, controlling for gender. The oculomotor items served as dependent variables and CAG repeat length and age as independent variables. A p-value of <0.05 was considered statistically significant.

Results

Demographic data are shown in Table 2. Premanifest HD gene carriers were significantly younger ($p < 0.001$) than controls and had a lower UHDRS-TMS ($p = 0.005$). In the control group, UHDRS-TMS was not related to age ($p = 0.271$). CAG repeat length was available for a minority of the controls, because it was not determined in non-related family controls and community controls who were not at risk for HD. Premanifest individuals closer to disease onset were older ($p = 0.002$), had a higher CAG expansion ($p < 0.001$), and a higher UHDRS-TMS ($p = 0.015$) compared to premanifest HD gene carriers further from disease onset.

All subjects scored 0 ‘normal’ or 1 ‘mild abnormality’ on the six oculomotor items of the UHDRS, and were therefore classified as ‘not affected’ or ‘affected’ respectively. Of the six oculomotor items, vertical ocular pursuit was the most frequently affected item in premanifest individuals (32.9%) as well as in controls (22.2%) (Table 3). Horizontal saccade velocity was not affected once in the entire group. When comparing all premanifest gene carriers to controls no statistically significant differences were found for the total UHDRS oculomotor score, or any of the six separate oculomotor items. However, when premanifest HD individuals near to disease onset were compared with healthy controls a significant difference was seen for horizontal ocular pursuit ($p = 0.044$, OR 13.100), with more premanifest individuals affected than controls. A similar trend was observed for

Table 2. Demographic data divided by gene status and expected years to HD onset

	PreHD (n = 70)	PreHD near (n = 35)	PreHD far (n = 35)	Controls (n = 27)	Controls versus preHD		PreHD near versus preHD far	
					MD/OR (95% CI)	*p*-value	MD/OR (95% CI)	*p*-value
Age, years	39.6 (±10.4)	43.4 (±9.9)	35.8 (±9.6)	50.9 (±13.5)	11.340 (6.238-16.442)	**<0.001**	7.571 (2.920-12.223)	**0.002**
Gender, male	23 (32.9%)	14 (40.0%)	9 (25.7%)	14 (51.9%)	0.454 (0.184-1.123)	0.084	1.926 (0.697-5.319)	0.203
CAG repeat length	42.1 (±2.4)	43.4 (±2.1)	40.8 (±2.0)	NA	NA	NA	2.571 (1.604-3.539)	**<0.001**
UHDRS-TMS	1.5 (±1.7)	2.0 (±1.8)	1.0 (±1.5)	2.7 (±2.0)	1.152 (0.357-1.948)	**0.005**	0.971 (0.193-1.750)	**0.015**

Data are mean (±standard deviation) for age, CAG repeat length, and UHDRS-TMS, and number (%) for gender. *p*-values were calculated using independent sample t-tests for age, CAG repeat length, and UHDRS-TMS, and Chi-square tests for gender. MD are given for age, CAG repeat length, and UHDRS-TMS; OR are given for gender. HD, Huntington's disease; PreHD, premanifest individuals; preHD near, premanifest individuals near to HD onset; preHD far, premanifest individuals far from HD onset; MD, mean difference; OR, odds ratio; CI, confidence interval; NA, not applicable; UHDRS-TMS Unified Huntington's Disease Rating Scale-Total Motor Score.

Table 3. Relationship of premanifest individuals and controls with the oculomotor items of the UHDRS

	PreHD (n = 70)	PreHD near (n = 35)	PreHD far (n = 35)	Controls (n = 27)	PreHD versus controls		PreHD near versus controls	
					OR/B (95% CI)	*p*-value	OR/B (95% CI)	*p*-value
Ocular pursuit horizontal, affected	8 (11.4%)	6 (17.1%)	2 (5.7%)	1 (3.7%)	11.325 (0.927-138.333)	0.057	13.100 (1.072-160.165)	**0.004**
Ocular pursuit vertical, affected	23 (32.9%)	15 (42.9%)	8 (22.9%)	6 (22.2%)	2.333 (0.719-7.570)	0.158	2.967 (0.896-9.823)	0.075
Saccade initiation horizontal, affected	3 (4.3%)	2 (5.7%)	1 (2.9%)	1 (3.7%)	4.019 (0.276-58.608)	0.309	3.991 (0.258-61.692)	0.322
Saccade initiation vertical, affected	8 (11.4%)	5 (14.3%)	3 (8.6%)	5 (18.5%)	0.918 (0.222-3.791)	0.906	1.003 (0.230-4.372)	0.996
Saccade velocity horizontal, affected	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA
Saccade velocity vertical, affected	1 (1.4%)	0 (0.0%)	1 (2.9%)	3 (11.1%)	0.128 (0.009-1.733)	0.122	<0.001	0.998
UHDRS total oculomotor score	0.61 (±0.997)	0.80 (±1.052)	0.43 (±0.917)	0.59 (±0.844)	-0.243 (-0.712-0.225)	0.305	-0.175 (-0.418-0.067)	0.154

Data are number (%) for the separate oculomotor items and mean (±standard deviation) for the UHDRS total oculomotor score. *p*-values were calculated using a logistic regression model for the separate oculomotor items and a linear regression model for the UHDRS total oculomotor score. Both models were controlled for age and gender. OR are given for the separate oculomotor items; B are given for the UHDRS total oculomotor score.

HD, Huntington's disease; UHDRS, Unified Huntington's Disease Rating Scale; PreHD, premanifest individuals; PreHD near, premanifest individuals near to HD onset; PreHD far, premanifest individuals far from HD onset; OR, odds ratio; B, beta; NA, not applicable.

Table 4. Relationship of CAG repeat length and age in premanifest individuals (n = 70) with horizontal and vertical ocular pursuit

	Ocular pursuit horizontal				Ocular pursuit vertical			
	Affected (n = 8)	Not affected (n = 62)	OR (95% CI)	*p*-value	Affected (n = 23)	Not affected (n = 47)	OR (95% CI)	*p*-value
CAG repeat length	42.1 (±2.1)	42.1 (±2.5)	1.227 (0.787-1.913)	0.366	42.5 (±3.0)	41.9 (±2.0)	1.229 (0.956-1.581)	0.107
Age, years	48.0 (±11.1)	38.5 (±9.9)	1.115 (1.021-1.219)	**0.016**	42.8 (±12.0)	38.0 (±9.3)	1.065 (1.006-1.127)	**0.030**

Data are mean (±standard deviation) for CAG repeat length and age. *p*-values were calculated using a logistic regression model, adjusting for gender.
OR, odds ratio; CI, confidence interval.

vertical ocular pursuit (p = 0.075, OR 2.967). Horizontal and vertical saccade initiation, and horizontal and vertical saccade velocity did not show any differences between the groups.

The relationship between the oculomotor items of the UHDRS and CAG repeat length and age was examined in premanifest individuals, controlling for gender. CAG repeat length was not related to horizontal and vertical ocular pursuit (Table 4). Age was significantly higher in the affected horizontal ocular pursuit group (p = 0.016, OR 1.115) and the affected vertical ocular pursuit group (p = 0.030, OR 1.065) compared to premanifest individuals without ocular pursuit deficits.

Discussion

In this cross-sectional study we showed that only horizontal ocular pursuit of the UHDRS oculomotor domain is affected in premanifest individuals near to HD onset compared to healthy controls. This is not the case when all premanifest HD gene carriers are compared with controls. This suggests that horizontal ocular pursuit is the only affected item of the six oculomotor items of the UHDRS in premanifest individuals. Vertical ocular pursuit showed a tendency towards the same.

Our demographic data showed that premanifest individuals near to HD onset were older, had a higher CAG expansion, and a higher UHDRS-TMS compared to premanifest HD gene carriers far from HD onset. These findings were expected, since age and CAG repeat length were used to calculate the expected years to HD onset according to the Langbehn formula.[14] The higher UHDRS-TMS found in controls compared to premanifest individuals is probably due to the higher age of the participants in this group, which has been reported before.[15] However, a linear regression analysis of the UHDRS-TMS as a function of age among controls did not show this correlation.

To our knowledge no study has been performed investigating the separate items of the oculomotor domain of the UHDRS in premanifest HD individuals and controls. Other cross-sectional reports using clinical oculomotor assessments only showed that premanifest individuals performed significantly worse compared to controls on the total score of the oculomotor domain of the UHDRS,[4] and on the overall oculomotor function, saccade velocity, and optokinetic nystagmus of the Quantified Neurologic Examination.[16] Our study did not find a difference for the total UHDRS oculomotor score between controls and premanifest individuals. This could be caused by a different definition used for premanifest HD individuals, which caused lower total oculomotor scores on the UHDRS-TMS in our study. Biglan et al.[4] used a diagnostic confidence level to identify premanifest individuals. As a result, individuals with an UHDRS-TMS higher than 5 were often defined

as premanifest, because participants were only defined as manifest when the examiner was more than 98 percent confident the participant had signs of HD. Accordingly, patients with a relatively high UHDRS-TMS were categorized as premanifest rather than manifest, while those same patients would have been categorized as manifest in our study. Our study's definition of premanifest HD, therefore, selects for lower UHDRS-TMS scores and, accordingly, the UHDRS total oculomotor scores were also lower in premanifest HD gene carriers in our study.

Differences found between controls and premanifest HD gene carriers are important, because they increase knowledge about early disease progression, and possibly indicate the first clinical signs present in premanifest HD. Since eye-tracking equipment is not practical in everyday clinical practice, it is relevant to know if the oculomotor items of the UHDRS are useful to detect early HD signs in patients. Our results suggest that horizontal ocular pursuit is the only affected oculomotor item in premanifest individuals and could be used to assess early clinical signs of HD in individuals who are at risk for developing HD. Vertical ocular pursuit was not significantly different between premanifest individuals close to disease onset and controls, but a trend was seen for this item as well. Horizontal and vertical saccade initiation, and horizontal and vertical saccade velocity did not show any differences between premanifest individuals and controls or between premanifest individuals close to disease onset and controls. Therefore these items of the UHDRS do not seem to contribute in detecting early disease signs. The fact that we did not find significant differences does not necessarily mean that they are not present, but might show that these items are not sensitive enough to defect deficits. Siesling et al.[17] also questioned the importance of the eye movements, because omitting saccade initiation and saccade velocity from the UHDRS-TMS only led to a small loss in correlation between the other items.

In contrast, other studies did find differences between premanifest individuals and controls for saccade initiation and saccade velocity.[5-8] However, these studies used eye-tracking equipment. They reported oculomotor abnormalities between premanifest HD gene carriers and controls, which consisted of more complex antisaccade and memory guided tasks, variability of latency, and error rates. However, in the TRACK-HD study,[18] antisaccade error rates in controls did not differ from those in premanifest individuals, only from those in premanifest individuals closer to predicted HD onset. Eye-tracking equipment did not show significant differences for horizontal and vertical pursuit tracking between premanifest individuals and controls.[5] Only one study compared results from eye-tracking equipment with clinical ratings of the UHDRS oculomotor section. Saccade initiation of the UHDRS was correlated with the average latency of saccades measured with the eye-tracking system. The correlation between the saccade velocity of the UHDRS and the measured velocity was not significant.[6]

In the second part of our study we examined the relationship between CAG repeat length and oculomotor abnormalities, and age and oculomotor abnormalities in premanifest HD individuals. Because saccade initiation and saccade velocity did not show differences between premanifest individuals and controls, we only examined ocular pursuit. We did not find a relationship between CAG repeat length and ocular pursuit. Age, however, was related to both horizontal and vertical ocular pursuit. This suggests that a clinician should be more aware of the possibility of affected ocular pursuit in older premanifest HD gene carriers. Especially since older individuals are more likely to be closer to HD onset.

A limitation of our study is the relatively small sample size and therefore the small number of participants who had oculomotor abnormalities. Secondly, the examiners were not blinded to the status of the participants. As a result, equivocal findings may have been graded as abnormal in premanifest HD gene carriers and normal in controls, thereby biasing results against the null hypothesis. Clinical examination of the oculomotor items of the UHDRS has its limitations due to difficulty in distinguishing between subtle possible pathology and normal eye movements, and due to interrater reliability. Previous studies have shown that the interrater reliability of the total UHDRS motor score is high, however they did not report the interrater reliability of the UHDRS oculomotor domain.[3,19] Additionally, eye movement abnormalities can have a nonspecific nature as well. Furthermore, we have tested multiple hypothesis without accounting for multiple comparisons. We did not correct for multiple comparisons because of the relatively small sample size and the likely presence of correlations between the different items. Accordingly, significant findings may be due to chance alone. If we want to decide whether or not the UHDRS oculomotor domain is as good as eye-tracking equipment to determine oculomotor abnormalities, these two assessments should be assessed together in an observational, prospective study.

Conclusions

In conclusion, we found that significantly more premanifest HD individuals near to disease onset had affected horizontal ocular pursuit compared to controls. This suggests that horizontal ocular pursuit is the only affected oculomotor item in premanifest individuals and could be used to assess early clinical signs of HD. Saccade initiation and saccade velocity do not seem useful for detecting differences between premanifest individuals and healthy controls. Therefore, when assessing individuals at risk for HD, these items of the UHDRS-TMS might be omitted. Our results also showed that higher age is related to horizontal and vertical ocular pursuit deficits in premanifest individuals. CAG repeat length was not related to oculomotor abnormalities.

References

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

2. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

3. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

4. Biglan KM, Ross CA, Langbehn DR, Aylward EH, Stout JC, Queller S, et al. Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study. Mov Disord 2009; 24: 1763–1772.

5. Blekher TM, Yee RD, Kirkwood SC, Hake AM, Stout JC, Weaver MR, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. Vision Re. 2004; 44: 2729–2736.

6. Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, et al. Saccades in presymptomatic and early stages of Huntington disease. Neurology 2006; 67: 394–399.

7. Antoniades CA, Altham PME, Mason SL, Barker RA, Carpenter R. Saccadometry: a new tool for evaluating presymptomatic Huntington patients. Neuroreport 2007; 18: 1133–1136.

8. Hicks SL, Robert MPA, Golding CVP, Tabrizi SJ, Kennard C. Oculomotor deficits indicate the progression of Huntington's disease. Prog Brain Res 2008; 171: 555–558.

9. Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 1993; 4: 387–392.

10. Stine OC, Pleasant N, Franz ML, Abbott MH, Folstein SE, Ross CA. Correlation between the onset age of Huntington's disease and length of the trinucleotide repeat in IT-15. Hum Mol Genet 1993; 2: 1547–1549.

11. Moschner C, Baloh RW. Age-related changes in visual tracking. J Gerontol 1994; 49: 235–238.

12. Seferlis F, Chimona TS, Papadakis CE, Bizakis J, Triaridis S, Skoulakis C. Age related changes in ocular motor testing in healthy subjects. J Vestib Res 2015; 25: 57–66.

13. Reilmann R, Roos R, Rosser A, Grimbergen Y, Kraus P, Craufurd D, et al. A teaching film, video library and online certification for the Unified Huntington's Disease Rating Scale Total Motor Score. Akt Neurol 2009; 36: 474.

14. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet 2004; 65: 267–277.

15. Cubo E, Ramos-Arroyo MA, Martinez-Horta S, Martinez-Descalls A, Calvo S, Gil-Polo C. Clinical manifestations of intermediate allele carriers in Huntington disease. Neurology 2016; 87: 1–8.

16. Kirkwood SC, Siemers E, Bond C, Conneally PM, Christian JC, Foroud T. Confirmation of subtle motor

changes among presymptomatic carriers of the Huntington disease gene. Arch Neurol 2000; 57: 1040–1044.

17. Siesling S, Zwinderman AH, Van Vugt JPP, Kieburtz K, Roos RAC. A shortened version of the motor section of the Unified Huntington's Disease Rating Scale. Mov Disord 1997; 12: 229–234.

18. Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RAC, Durr A, Craufurd D, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009; 8: 791–801.

19. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

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CHAPTER 4

Assessment scales for patients with advanced Huntington's disease: comparison of the UHDRS and UHDRS-FAP

Abstract

Background: The standard clinical assessment tool in Huntington's disease is the Unified Huntington's Disease Rating Scale (UHDRS). In patients with advanced Huntington's disease ceiling and floor effects of the UHDRS hamper the detection of changes. Therefore, the UHDRS-For Advanced Patients (UHDRS-FAP) has been designed for patients with late stage Huntington's disease.

Objectives: This cross-sectional study aims to examine if the UHDRS-FAP can differentiate better between patients with advanced Huntington's disease than the UHDRS.

Methods: Forty patients, who were institutionalized or received day-care, were assessed with the UHDRS, UHDRS-FAP, and Care Dependency Scale (CDS). The severity of Huntington's disease was defined by the Total Functional Capacity (TFC). Comparisons between consecutive TFC stages were performed for all domains of the UHDRS, UHDRS-FAP, and CDS using Mann-Whitney U tests.

Results: The motor scores of the UHDRS-FAP and UHDRS were the only subscales with significantly worse scores in TFC stage 5 compared to stage 4. In TFC stages 4-5, the range of the UHDRS-FAP motor score was broader, the standard error of measurement was lower, and the effect size r was higher than for the UHDRS motor score. The CDS declined significantly across all TFC stages.

Conclusions: Our results suggest that the UHDRS-FAP motor score might differentiate better between patients with severe Huntington's disease than the UHDRS motor score. Therefore, the UHDRS-FAP motor score is potentially a better instrument than the UHDRS motor score to improve disease monitoring and, subsequently, care in patients with advanced Huntington's disease in long-term care facilities.

Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder caused by an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat in the Huntingtin gene on chromosome 4.[1] The disease is clinically characterized by disorders of movement, cognition, and behavior. Progression of HD into more advanced stages ultimately leads to functional decline. The mean age at disease onset is between 30 and 50 years and the mean duration of HD is 17 to 20 years.[2]

The standard clinical assessment tool in HD is the Unified Huntington's Disease Rating Scale (UHDRS).[3] The UHDRS has been developed to monitor disease progression in individual patients, and is used in research and in clinical practice. The UHDRS has demonstrated to be sensitive to detect longitudinal changes in manifest HD patients.[3-8]

In more advanced stages of HD, knowledge is limited about the course of the clinical manifestations. There is a lack of sensitive disease outcome measures to track disease progression and guidelines for symptom management in late stage care.[9] Ceiling and floor effects of the UHDRS hamper the detection of changes in patients with advanced HD.[8] This limitation makes disease monitoring difficult and complicates the measurement of effect of therapeutic interventions in advanced HD. Therefore, the UHDRS-For Advanced Patients (UHDRS-FAP) has been designed for patients with late stage HD.[10] The authors showed that both the UHDRS and the UHDRS-FAP detected a decline in patients with advanced HD. However, the UHDRS-FAP appeared to be more sensitive to change and was the only scale that detected a decline in patients with a very low functional capacity.[10]

Although the UHDRS-FAP was shown to be more sensitive to detect decline than the UHDRS when assessed longitudinally in patients with advanced HD, it is not implemented yet on a larger scale in long-term care facilities and little is known about its cross-sectional properties. Therefore, we aim to explore its capacity to differentiate between the later stages of the disease on the basis of cross-sectional data in one long-term care facility. We also aim to confirm previous findings about the internal consistency and interrater reliability of both scales.

Methods

Participants and setting

All patients (n = 90) with a clinically and/or genetically confirmed diagnosis of HD, who were institutionalized or received day-care at the Huntington Center Topaz Overduin (Katwijk), were asked to participate in this study. Patients had to be older than 18 years of age. Exclusion criteria were a central nervous system disorder other than HD and participation in an interventional medical trial during the study. Forty patients were able and willing to participate. The local medical ethics committee approved the study and written informed consent was obtained from all participants or their caregivers. Huntington Center Topaz Overduin is a nursing home specialized in the care for HD patients, both in late and early stages, with 70 beds and over 100 outpatients. Specialized medical doctors, psychologists, therapists, and nursing personnel provide long-term care and day-care in the nursing home, organize activities, and offer support for patients who live at home. This study was carried out in 2017. On the same day, patients were first assessed with the UHDRS followed by the UHDRS-FAP. Both scales were administered twice by two independent medical doctors experienced with HD with an intended interval of seven days.

Assessments

The UHDRS is divided into four domains: motor performance, cognitive function, behavioral abnormalities, and functional abilities.[3] The motor section consists of 31 items assessing oculomotor, bradykinesia/rigidity, dystonia, chorea, and gait/balance.[3] The items are rated from zero to four, with zero indicating normal findings and four indicating severe abnormalities. The range of the Total Motor Score (TMS) is 0 to 124, with higher scores indicating more severe motor impairment. The cognitive component includes the Verbal Fluency test,[11] the Symbol Digit Modalities test,[12] and the Stroop test (color naming, word reading, and interference).[13] Lower scores indicate worse cognitive performance. The behavioral assessment measures the frequency and severity of 11 items, which are rated from zero (almost never/absent) to four (almost always/severe).[3] The items assess depression, anxiety, aggression, psychosis, and other behavioral abnormalities. The behavioral score ranges from 0 to 88, with higher scores indicating more severe psychiatric abnormalities. The functional domain comprises three components, namely the Total Functional Capacity (TFC), the Functional Assessment Scale (FAS), and the Independence Scale (IS).[3] The TFC consists of five items (occupation,

finances, domestic chores, activities of daily living, and care level) and ranges from 0 to 13.[14] The FAS includes 25 yes/no questions about common daily tasks (range 0-25). The IS measures the level of independence by one single score between 10 and 100. For all functional scores, lower scores indicate a worse function.

The UHDRS-FAP consists of four sections, which are the motor, cognitive, somatic, and behavioral sections.[10] The motor domain comprises 14 items assessing frequency of falling, dysphagia, muscle contractures, and the capacity to eat, dress, and wash independently, as well as other motor components (range 0-52). Cognitive function is measured by functional and categorical matching of the Protocole Toulouse Montreal d'Evaluation des Gnosies Visuelles (PEGV),[15] pointing, simple commands, the Stroop test, orientation, participation in activities, imitation (apraxia), and automatic series. The somatic subscale includes ten items assessing hyperhidrosis, hypersalivation, incontinence, digestion, hypersomnia, and pressure ulcers (range 0-28). The behavioral score consists of eight yes/no questions about the presence of psychiatric abnormalities (range 0-8). For the motor, somatic, and behavioral section, higher scores indicate more impairment, and for the cognitive section, lower scores indicate worse performance.

Nurses directly involved in patient care completed the Care Dependency Scale (CDS).[16] The CDS is a questionnaire of 15 items assessing different aspects of dependency on care in daily activities (eating and drinking, incontinence, mobility, communication, and other care items). The total CDS score ranges from 15 (completely dependent on care) to 75 (almost independent of care).

Statistical analysis

IBM Statistical Package for the Social Sciences (SPSS) version 23 was used for data analysis. Internal consistency was assessed in all subscales of the UHDRS and the UHDRS-FAP for all first evaluations using Cronbach's alpha (α). Interrater reliability of each section of both scales was calculated by the intraclass correlation coefficient (ICC). We used a two-way random model with absolute agreement. The motor, cognitive, and behavioral sections of the UHDRS-FAP were compared with the motor, cognitive, and behavioral sections of the UHDRS using Spearman's rank correlation coefficients (ρ). Again, we used the scores of all first evaluations. An ICC, Cronbach's α, or ρ higher than 0.7 was considered good and lower than 0.4 was defined as poor.[17,18] Severity of HD was divided into five stages using the TFC subscale of the UHDRS: stage 1 (TFC 11-13), stage 2 (TFC 7-10), stage 3 (TFC 3-6), stage 4 (TFC 1-2), and stage 5 (TFC 0).[14] A higher TFC stage indicates worse functional capacity. The participants were classified according to their TFC stage and the median

scores of each section of the UHDRS, UHDRS-FAP, and CDS were calculated per stage. Comparisons of the UHDRS and UHDRS-FAP domains and the CDS were performed across the different TFC stages using Mann-Whitney U tests. For all comparisons, we used the scores of the first evaluations. A *p*-value of <0.05 was considered statistically significant. For the higher TFC stages, we also calculated the effect size (r), the range and the standard error of measurement (SEM) of the motor section of both scales to examine which scale differentiates better in more advanced HD. A higher r, broader range, and lower SEM suggested a better differentiation between patients.

Results

Forty patients with advanced HD participated in this study. Age and gender of study participants were similar to the age and gender of the patients who did not consent to participate in the study. In the nursing home unit specialized in psychiatric problems and the unit with patients highly dependent on care, less patients chose to participate in the study (35% and 31%, respectively) than in the unit with patients less dependent on care and the day-care department (57% and 60%, respectively). Participants were assessed twice by two independent raters. Time between the two evaluations was 7 to 23 days (median of seven days). The second time 37 patients participated; two patients found the assessments too confrontational and one had died. Demographic data of the 40 participants are reported in Table 1. CAG repeat length was missing for two patients, because they were tested for HD through linkage analysis before the identification of the Huntingtin gene in 1993. Medication for HD symptoms, such as antidepressants, antipsychotics, tetrabenazine, and benzodiazepines, was used by 95% of the patients. Medication was stable between the two evaluations. Mean scores of the separate sections of the UHDRS and UHDRS-FAP are reported in Table 2.

Internal consistency was high for the motor score ($\alpha = 0.966$), cognitive score ($\alpha = 0.937$), and FAS ($\alpha = 0.945$) of the UHDRS and for the motor score ($\alpha = 0.902$) and cognitive score ($\alpha = 0.857$) of the UHDRS-FAP (Table 3). The behavorial score of the UHDRS-FAP had a low internal consistency ($\alpha = 0.347$). Interrater reliability was calculated for the two raters who examined both 37 HD patients. Moderate ICC values were found for the behavioral score of both the UHDRS and UHDRS-FAP (0.681 and 0.503, respectively; Table 3). ICC values were high for all other subscales of the UHDRS and UHDRS-FAP. Interrater reliability of the UHDRS-FAP motor score (ICC = 0.954) was higher than for the UHDRS-TMS (ICC = 0.876). The motor, cognitive, and behavioral domains of the UHDRS-FAP correlated strongly with the corresponding domains of the UHDRS ($\rho = 0.860$, $\rho = 0.991$, and $\rho = 0.714$, respectively).

Table 1. Demographic data of all participants (n = 40)

Age, years	54.5 (±12.8)
Male/female (% male)	14/26 (35.0%)
CAG repeat length (n = 38)	44.8 (±3.8)
Educational level, years	13.3 (±2.9)
Age of disease onset, years	40.7 (±11.3)
Disease duration, years	13.4 (±5.1)
Nursing home/day-care (% nursing home)	28/12 (70.0%)

Data are mean (± standard deviation) for age, CAG repeat length, educational level, age of disease onset and disease duration, and number (%) for male/female and nursing home/day-care.

Table 2. Clinical characteristics of all participants (n = 40)

	UHDRS		UHDRS-FAP	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max
Motor score	64.2 (±26.1)	0-124	14.9 (±11.3)	0-52
Cognitive score	78.1 (±64.6)	0-∞	109.8 (±65.4)	0-∞
Behavioral score	15.5 (±8.9)	0-88	1.8 (±1.4)	0-8
Somatic score			6.9 (±6.0)	0-28
Total Functional Capacity	2.6 (±2.3)	0-13		
Functional Assessment Scale	9.6 (±6.7)	0-25		
Independence Scale	55.5 (±16.9)	10-100		

Mean scores are given for all sections of the UHDRS and UHDRS-FAP.
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation; UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients.

Median scores of the UHDRS and UHDRS-FAP sections and the CDS for the different TFC stages are shown in Table 4. The UHDRS-TMS was significantly different between all consecutive TFC stages, while the motor score of the UHDRS-FAP was only significantly different between TFC stages 3 and 4 ($p < 0.001$), and between TFC stages 4 and 5 ($p = 0.019$; i.e., the scores were significantly worse in patients with more advanced HD). In TFC stages 4 and 5, the effect size r was higher for the UHDRS-FAP motor score compared to the UHDRS-TMS (0.525 and 0.466, respectively). The proportion of the range of the UHDRS-FAP motor score that was covered was broader than for the UHDRS-TMS (17.9% and 8.9%, respectively), and the SEM was lower (1.89 and 5.63, respectively) in TFC stages 4 and 5. The cognitive section of both scales was only significantly different between TFC

Table 3. Internal consistency (n = 40) and interrater reliability (n = 37) of the UHDRS and UHDRS-FAP

	UHDRS		UHDRS-FAP	
	Cronbach's α	ICC (95% CI)	Cronbach's α	ICC (95% CI)
Motor score	0.966	0.876 (0.774-0.934)	0.902	0.954 (0.904-0.977)
Cognitive score	0.937	0.981 (0.963-0.990)	0.857	0.984 (0.968-0.991)
Behavioral score	0.682	0.681 (0.462-0.822)	0.347	0.503 (0.226-0.707)
Somatic score			0.717	0.759 (0.580-0.869)
Total Functional Capacity	0.608	0.938 (0.876-0.968)		
Functional Assessment Scale	0.945	0.958 (0.917-0.979)		
Independence Scale	NA	0.842 (0.626-0.927)		

Internal consistency is expressed by Cronbach's α and interrater reliability by ICC. ICC values were calculated using a two-way random model with absolute agreement.
Abbreviations: α, alpha; CI, confidence interval; ICC, intraclass correlation coefficient; NA, not applicable; UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients.

Table 4. UHDRS and UHDRS-FAP scores across different TFC stages

		TFC stage 2 (n = 4)	TFC stage 3 (n = 16)	TFC stage 4 (n = 10)	TFC stage 5 (n = 10)	*p*-value for TFC2 vs TFC3	*p*-value for TFC3 vs TFC4	*p*-value for TFC4 vs TFC5
Motor score	UHDRS	25.0 (24.3-37.8)	41.5 (35.8-61.3)	82.5 (71.3-86.3)	90.0 (79.5-97.0)	**0.022**	**<0.001**	**0.035**
	UHDRS-FAP	4.0 (1.3-6.8)	6.0 (3.0-8.8)	19.5 (12.0-23.0)	27.5 (22.3-37.3)	0.335	**<0.001**	**0.019**
Cognitive score	UHDRS	152.0 (107.5-202.5)	106.0 (72.8-167.0)	40.5 (31.0-53.3)	3.0 (0.0-47.3)	0.249	**<0.001**	0.105
	UHDRS-FAP	171.8 (145.8-216.5)	146.5 (118.3-192.5)	73.8 (64.4-91.5)	30.8 (0.8-85.6)	0.385	**<0.001**	0.075
Behavioral score	UHDRS	14.5 (7.3-27.8)	11.0 (4.8-23.0)	17.0 (11.0-26.3)	15.0 (8.0-26.0)	0.682	0.150	0.684
	UHDRS-FAP	1.5 (0.0-3.0)	1.0 (0.0-2.8)	1.5 (1.0-3.0)	2.0 (1.8-3.3)	>0.999	0.201	0.353
Somatic score	UHDRS-FAP	3.0 (1.0-5.8)	3.0 (2.0-5.5)	6.5 (2.5-15.3)	12.5 (5.5-15.5)	0.750	0.135	0.393
CDS		68.5 (65.8-69.8)	61.5 (56.5-65.5)	40.0 (36.0-41.5)	31.0 (17.8-35.8)	**0.016**	**<0.001**	**0.015**

Data are median (with interquartile range) for the different sections of the UHDRS and UHDRS-FAP, and CDS. *p*-values were calculated using Mann-Whitney U tests. Significant differences ($p < 0.05$) are shown in bold.

Abbreviations: CDS, Care Dependency Scale; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients.

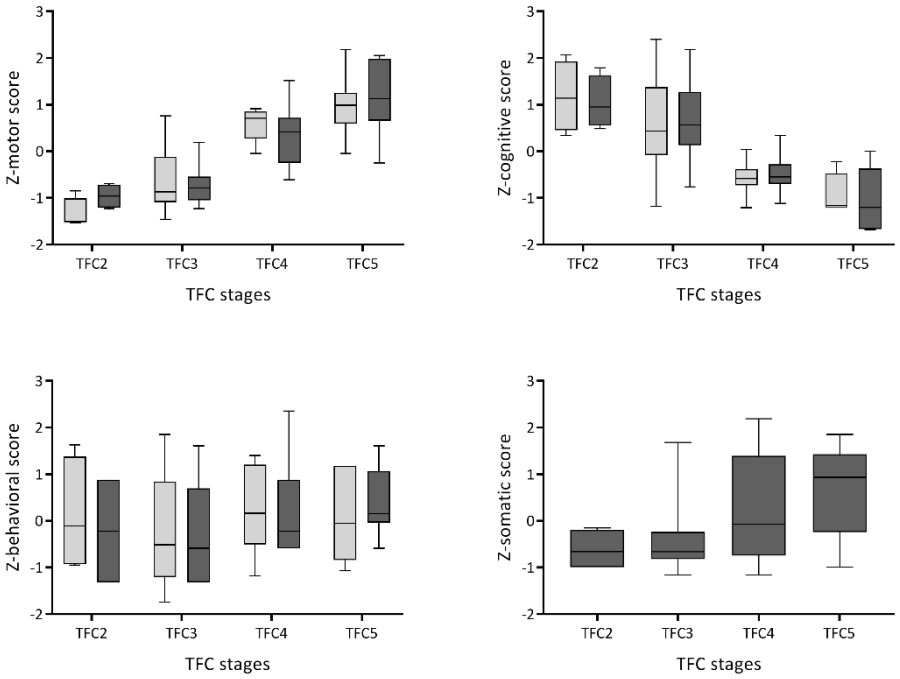

Figure 1. Z-scores of the motor, cognitive, behavioral, and somatic scores of the Unified Huntington's Disease Rating Scale (UHDRS; light grey) and the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP; dark grey) across the Total Functional Capacity (TFC) stages.

stages 3 and 4. The behavioral score of both the UHDRS and UHDRS-FAP and the somatic score did not show any differences between the TFC stages. The CDS declined significantly across all TFC stages. Z-scores of the motor, cognitive, behavioral, and somatic scores of the UHDRS and UHDRS-FAP across the TFC stages are also presented in Fig 1.

Discussion

This study in advanced HD patients demonstrated that the UHDRS-FAP motor score and the UHDRS-TMS were the only subscales with a significantly worse score in TFC stage 5 compared to stage 4. The scores of the other UHDRS-FAP and UHDRS sections did not differ between TFC stages 4 and 5, suggesting that the UHDRS-FAP motor score and the UHDRS-TMS are the only subscales that can differentiate between patients in high TFC

stages. However, in TFC stages 4 and 5, the range of the UHDRS-FAP motor score was broader, the SEM was lower, and the effect size r was higher than for the UHDRS-TMS. These findings suggest that the motor score of the UHDRS-FAP might differentiate better between patients with advanced HD than the UHDRS-TMS. Therefore, this scale could avoid the ceiling effect sometimes seen in the UHDRS-TMS and subsequently, prove more beneficial in research and clinical care of patients with very advanced HD. Furthermore, implementation of the UHDRS-FAP motor score in daily practice could improve disease monitoring and, therefore, care in patients with advanced HD residing in long-term care facilities. In particular, when a new patient is admitted to a nursing home, this score can serve as a screening instrument and provide information about motor performance and care needed. The motor score of the UHDRS-FAP can easily be administered in nursing homes and only takes a few minutes to complete. Multiple longitudinal studies have reported an increase of the UHDRS-TMS during follow-up. However, these studies did not differentiate between different TFC stages, and the patients were in a less advanced HD stage.[3-6] Another study, in which a longitudinal assessment of the UHDRS-FAP and UHDRS was performed, showed an increase of the motor score in both scales over time, with a steeper slope for the UHDRS-FAP than for the UHDRS.[10] Moreover, in patients with TFC scores ≤ 1, only the UHDRS-FAP motor score deteriorated, whereas the UHDRS-TMS did not, confirming the UHDRS-TMS ceiling effect in advanced HD.

We showed that the cognitive score of the UHDRS and UHDRS-FAP differed significantly between TFC stages 3 and 4, but not between TFC stages 4 and 5. This finding suggests that the cognitive domain of both scales is informative in the middle stages of HD, but not in the late stages. Therefore, the usefulness of assessment of cognition in very advanced HD should be questioned. A longitudinal study on cognitive performance across the TFC stages showed that the cognitive tests of the UHDRS declined significantly in consecutive TFC stages, except from TFC stage 4 to 5.[19] This also implies that cognitive assessment is not useful in late stage HD, or at least the scale is not sensitive enough to detect differences. Youssov et al. also reported that the cognitive section of the UHDRS did not decline over time in patients with low functional capacity (TFC scores ≤ 1). However, the cognitive section of the UHDRS-FAP did decline when assessed longitudinally.[10]

The behavioral section of the UHDRS and UHDRS-FAP did not differ between any of the consecutive TFC stages in our study, suggesting that behavioral abnormalities do not progress when HD becomes more severe. However, this could be caused partly by less communicative abilities of patients in late stage HD. Studies of the Problem Behaviors Assessment (PBA), an adjusted version of the UHDRS behavioral section, showed that only apathy is related to disease duration.[20,21] Depression and irritability were not related to disease stage. Several studies found that the UHDRS behavioral section did not correlate with the other sections of the UHDRS,[3,10,22] which also suggests that psychiatric

abnormalities do not progress across the disease stages. Furthermore, longitudinal assessment of the behavioral domain of the UHDRS and UHDRS-FAP did not show deterioration over time.[4-6,10] Only in a subgroup of HD patients did the UHDRS-FAP behavioral score worsen over time.[10] The results of our study suggest that the behavioral sections of the UHDRS and UHDRS-FAP are not useful to differentiate between the TFC stages. However, for clinical care an estimation of a patient's behavioral disturbances is relevant and, therefore, the behavioral section is useful for clinical care.

The CDS is completed by nursing personnel and has previously been validated in patients with dementia in long-term care facilities. Our study in HD patients showed a similar mean score (HD: 47.9, dementia: men 47.5, women 43.0) and internal consistency (HD: Cronbach's α = 0.961, dementia: Cronbach's α = 0.97) for the CDS as in patients with dementia.[16,23] This suggests that the CDS could also be applied in the care for HD patients in nursing homes.

We found a high internal consistency for the motor score, cognitive score, and FAS of the UHDRS and for the motor score and cognitive score of the UHDRS-FAP, which confirmed previous findings.[3,10] The behavorial score of the UHDRS-FAP had a low internal consistency (Cronbach's α = 0.347), which is far below the generally accepted value for use in research (0.7).[17,18] A previous study on the UHDRS-FAP also reported that the internal consistency of the UHDRS-FAP behavioral score (Cronbach's α = 0.49) was lower than that of the UHDRS-FAP motor and cognitive score.[10] The low internal consistency might be explained by the fact that the behavioral score of the UHDRS-FAP only consists of eight yes/no questions. Interrater reliability was high for all subscales of the UHDRS and UHDRS-FAP, except for the behavioral subscales. Several studies found similar ICC values for the motor and cognitive domains of the UHDRS and UHDRS-FAP.[3,10] However, due to the day to day variation of signs within a patient, the time between the two examinations by the two raters (median of seven days) may have affected the interrater reliability in our study. Furthermore, the short retest interval may have influenced the cognitive performance the second time and therewith the interrater reliability due to a possible learning effect.[24,25] Moderate ICC values were found for the behavioral subscale of both the UHDRS and UHDRS-FAP (0.681 and 0.503, respectively). This contradicts previous studies, which found high interrater reliability (0.73-0.99).[10,20,21] However, two of these previous studies used the PBA instead of the UHDRS behavioral section and calculated a "clinically relevant" interrater reliability, which means only differences larger than one point were included.[20,21] As expected, we found high correlations between the motor, cognitive, and behavioral domain of the UHDRS and the UHDRS-FAP.

The strengths of our study are the administration of both the UHDRS and UHDRS-FAP on the same day, so there is no variation within a patient, and that both raters received

training to perform the UHDRS. A limitation of this study is that due to practical reasons, the first assessment was not consistently performed by the same medical doctor, which may have caused variability in the outcome of the UHDRS and UHDRS-FAP scores. Each medical doctor examined about half of the patients first. Another limitation is the small sample size, especially in TFC stage 2. However, patients in this TFC stage are usually not classified as advanced. Additionally, our study reports only cross-sectional results. Longitudinal assessment of the UHDRS-FAP is necessary to examine if the scale is sensitive enough to detect changes within patients over time.

In conclusion, in patients with advanced HD, the UHDRS-FAP motor score can be used to differentiate between patients in TFC stages 4 and 5. Therefore, this subscale can possibly improve disease monitoring and, subsequently, care in patients with advanced HD in long-term care facilities. Cognitive and behavioral assessments do not seem useful for differentiating between patients in late stage HD (TFC stages 4 and 5). However, behavioral evaluation is useful for clinical care.

References

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

2. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

3. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

4. Siesling S, Van Vugt JPP, Zwinderman KAH, Kieburtz K, Roos RAC. Unified Huntington's Disease Rating Scale: a follow up. Mov Disord 1998; 13: 915–919.

5. Meyer C, Landwehrmeyer B, Schwenke C, Doble A, Orth M, Ludolph AC. Rate of change in early Huntington's disease: a clinicometric analysis. Mov Disord 2012; 27: 118–124.

6. Toh EA, MacAskill MR, Dalrymple-Alford JC, Myall DJ, Livingston L, Macleod SAD, et al. Comparison of cognitive and UHDRS measures in monitoring disease progression in Huntington's disease: a 12-month longitudinal study. Transl Neurodegener 2014; 3: 15.

7. Feigin A, Kieburtz K, Bordwell K, Como P, Steinberg K, Sotack J, et al. Functional decline in Huntington's disease. Mov Disord 1995; 10: 211–214.

8. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

9. Simpson SA. Late stage care in Huntington's disease. Brain Res Bull 2007; 72: 179–181.

10. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

11. Benton AL, Hamsher K DeS. Multilingual aphasia examination manual. Iowa City: Univ Iowa, 1978.

12. Smith A. Symbol digit modalities test manual. Los Angeles: West Psychol Serv, 1973.

13. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643–662.

14. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

15. Agniel A, Joanette Y, Doyon B, Duchein C. Protocole Montreal-Toulouse d'Evaluation des Gnosies Visuelles. Fr L'Ortho Ed, 1992.

16. Dijkstra A, Buist G, Moorer P, Dassen T. Construct validity of the Nursing Care Dependency Scale. J Clin Nurs 1999; 8: 380–388.

17. Nunnally JC, Bernstein IH. Psychometric Theory, 3rd edition. New York: McGraw-Hill, 1994.

18. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994; 6: 284–290.

19. Baake V, Reijntjes RHAM, Dumas EM, Thompson JC, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017; 95: 51–62.

20. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 219–226.

21. Kingma EM, Van Duijn E, Timman R, Van der Mast RC, Roos RAC. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008; 30: 155–161.

22. Klempir J, Klempirova O, Spackova N, Zidovska J, Roth J. Unified Huntington's Disease Rating Scale: clinical practice and a critical approach. Funct Neurol 2006; 21: 217–221.

23. Caljouw MAA, Cools HJM, Gussekloo J. Natural course of care dependency in residents of long-term care facilities: prospective follow-up study. BMC Geriatr 2014; 14: 67.

24. Beglinger LJ, Adams WH, Fiedorowicz JG, Duff K, Langbehn D, Biglan K, et al. Practice effects and stability of neuropsychological and UHDRS tests over short retest intervals in Huntington disease. J Huntingtons Dis 2015; 4: 251–260.

25. Schramm C, Katsahian S, Youssov K, Démonet J-F, Krystkowiak P, Supiot F, et al. How to capitalize on the retest effect in future trials on Huntington's disease. PLoS One 2015; 10.

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CHAPTER 5

Longitudinal assessment of the Unified Huntington's Disease Rating Scale (UHDRS) and UHDRS-For Advanced Patients (UHDRS-FAP) in patients with late stage Huntington's disease

Abstract

Background and purpose: Symptoms and signs in patients with Huntington's disease are usually assessed with the Unified Huntington's Disease Rating Scale (UHDRS). Ceiling and floor effects hamper the measurement of disease progression in patients with late stage Huntington's disease and therefore the UHDRS-For Advanced Patients (UHDRS-FAP) has been developed. The aim of this longitudinal study is to examine if the UHDRS-FAP and UHDRS are sensitive enough to detect change over time in late stage Huntington's disease.

Methods: Forty nursing home residents and patients receiving day-care were assessed with the UHDRS, UHDRS-FAP, and Care Dependency Scale (CDS). After six months, the assessment scales were completed again in 29 patients. Changes between baseline and follow-up were calculated using paired t-tests. Wilcoxon signed-rank tests were used to calculate longitudinal changes for middle and late stage patients separately.

Results: The motor and cognitive score of the UHDRS-FAP deteriorated during six months' follow-up, whilst the motor and cognitive score of the UHDRS did not show change. Two functional domains of the UHDRS and the CDS also declined. The behavioral score significantly improved with both rating scales in late stage patients.

Conclusions: Our results suggest that the UHDRS-FAP motor and cognitive score, the functional domains of the UHDRS, and the CDS can detect disease progression in late stage Huntington's disease. Therefore, the use of these scores in nursing homes is recommended to optimize care by monitoring disease progression and by evaluating the effect of interventions in clinical care. Psychiatric symptoms seem to fade away as the disease progresses.

Introduction

Huntington's disease (HD) is a neurodegenerative disorder characterized by progressive motor impairment, cognitive decline, and psychiatric symptoms. It is caused by an autosomal dominantly inherited cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene on chromosome 4.[1] HD usually becomes manifest around the age of 30-50 years and mean disease duration is 17-20 years.[2] As the disease progresses, the symptoms lead to functional decline and loss of independency, which may require nursing home admission.

Presence, severity and progression of symptoms and signs in HD patients are usually assessed with the Unified Huntington's Disease Rating Scale (UHDRS), which is subdivided into motor, cognitive, behavioral and functional domains.[3] Several studies have shown that the motor, cognitive and functional sections of the UHDRS can detect longitudinal changes in manifest HD patients.[3-8] However, in late stage HD ceiling and floor effects of the UHDRS hamper the detection of changes[8,9] and therefore disease progression is challenging to measure in patients with advanced HD, both in clinical practice and in research. For patients with late stage HD the UHDRS-For Advanced Patients (UHDRS-FAP) has been developed, which consists of motor, cognitive, somatic and behavioral sections.[10] The developers of the scale have performed a longitudinal study of the UHDRS-FAP, which showed that the motor, cognitive and somatic scores deteriorated over time.[10] The behavioral score only worsened in a subgroup of HD patients.

Recently, our cross-sectional study concerning the sensitivity of the UHDRS and UHDRS-FAP in patients with advanced HD showed that only the motor scores of the UHDRS and UHDRS-FAP could differentiate between patients with very low functional capacity.[11] The cognitive, behavioral and somatic subscales did not differ between patients with low functional abilities. With this follow-up study, the aim is to examine if the UHDRS-FAP and UHDRS are sensitive enough to detect change over time in late stage HD.

Methods

Participants and setting

Nursing home residents and patients receiving day-care at the Huntington Center Topaz Overduin (Katwijk, the Netherlands) were invited to participate in this study. The Huntington Center Topaz Overduin is specialized in care for HD patients and comprises a

nursing home with 70 residents, a day-care facility with 20 patients, and an outpatient clinic with over 100 patients. Inclusion criteria were a clinically and/or genetically confirmed diagnosis of HD and age above 18 years. Exclusion criteria comprised a central nervous system disorder other than HD or current participation in an interventional medical trial. The medical ethics committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all participants or their caregivers. The participants were first assessed with the UHDRS followed by the UHDRS-FAP on the same day. Preferably, the caregivers of the patients were present when the scales were assessed. After six months both scales were completed again. The rating scales were administered by two medical doctors, who were both UHDRS certified. Nursing personnel completed the Care Dependency Scale (CDS) for all participants at both time points.[12]

Assessments

The motor section of the UHDRS, which is also called the UHDRS-Total Motor Score (UHDRS-TMS), is composed of 31 items ranging from 0 (not affected) to 4 (severely affected).[3] Oculomotor function, bradykinesia/rigidity, chorea, dystonia, and gait/balance are examined. The UHDRS-TMS ranges from 0 to 124, with higher scores indicating worse motor performance. Cognitive function is tested with the Verbal Fluency test, the Symbol Digit Modalities test, and the Stroop test (color naming, word reading, and interference). Lower scores indicate worse cognitive function. Behavioral abnormalities are assessed by 11 items, such as depression, anxiety, irritability/aggression, obsessive-compulsive behaviors, psychosis and apathy. Each item is rated for severity and frequency from 0 to 4 and the range of the total score is 0-88, with higher scores indicating more severe psychiatric symptoms. Functional ability is measured by three subsections: Total Functional Capacity (TFC), the Functional Assessment Scale (FAS), and the Independence Scale (IS). TFC is a 5-item questionnaire concerning occupation, handling finances, domestic chores, activities of daily living and level of care, which ranges from 0 to 13.[13] The FAS is a questionnaire with 25 yes/no items, which screens an individual's capacity to complete specific tasks independently (range 0-25). The IS assesses functional ability with one single score, ranging from 10 (tube-fed, total bed care) to 100 (no special care needed). For the three functional scores, lower scores indicate more functional decline.

The motor domain of the UHDRS-FAP consists of 14 items, such as walking around, capacity to transfer, eat, and wash independently, dysphagia, and tendon retraction (range 0-52).[10] The cognitive score comprises functional and categorical matching of the Protocole Toulouse Montreal d'Evaluation des Gnosies Visuelles (PEGV)[14], pointing, simple

commands, the Stroop test, orientation, participation in activities, imitation (apraxia) and automatic series. Somatic symptoms are measured by 10 items, which are hyperhidrosis, hypersalivation, incontinence, digestion, hypersomnia and pressure ulcers (range 0-28). Behavioral abnormalities are examined by 8 yes/no items about the presence of psychiatric symptoms (range 0-8). Higher scores on the motor, somatic and behavioral domains indicate a higher level of impairment. For the cognitive domain, lower scores indicate more cognitive decline.

The CDS is a questionnaire completed by nurses and includes 15 items on different aspects of care dependency, such as eating and drinking, day-night rhythm, dressing, avoiding danger, and learning ability.[12] All items are rated on a 1-5 point scale, resulting in a total score ranging from 15 (completely dependent on care) to 75 (almost independent of care).

Statistical analysis

Demographic data and mean scores of the UHDRS and UHDRS-FAP domains and CDS were calculated at baseline. At follow-up six months later, the mean scores were calculated again and compared with baseline for the patients who participated twice using paired t-tests. Change over time was also calculated for the different tests of the UHDRS cognitive section separately, since these assessments measure different elements of cognition. Responsiveness of the domains was determined by effect sizes (ESs) and standardized response means (SRMs). An ES of 0.20 was considered small, an ES of 0.50 moderate and an ES of 0.80 large.[15] Additionally, participants were classified according to their TFC stage. TFC stages define the severity of HD and derive from the TFC subscale of the UHDRS: stage 1, TFC 11-13; stage 2, TFC 7-10; stage 3, TFC 3-6; stage 4, TFC 1-2; stage 5, TFC 0.[13] Higher TFC stages indicate worse functional capacity. Longitudinal changes of the UHDRS and UHDRS-FAP subscores and CDS score were calculated for TFC stage 4-5 (late stage) and TFC stage 2-3 (middle stage) using Wilcoxon signed-rank tests. A p-value of <0.05 was considered statistically significant. Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS, Leiden, The Netherlands) version 23.

Results

At baseline 40 HD patients participated in our study. After six months, 29 of them participated again, of whom 21 resided in a long-term care facility and 8 received day-care. Eleven patients were lost to follow-up due to death (three), participation in an interventional medical trial (one) or withdrawal of consent (seven) for the following

reasons: assessments too confrontational (three) or too exhausting (two), or deterioration of HD (two). Demographic data at baseline are shown in Table 1 for all 40 participants and for the 29 patients who participated twice. Demographics at baseline were similar between the two groups. At baseline and follow-up 27 of the 29 patients used medication for HD symptoms, such as antidepressants, antipsychotics, and tetrabenazine. Medication was stable between the two evaluations in 18 patients and changed in 9 patients (starting or stopping medication, increase or decrease in dosage, or a combination of these options). Change in medication was equally distributed across the TFC stages.

Table 2 reports the mean scores of all sections of the UHDRS, UHDRS-FAP and CDS at baseline and follow-up. Mean time interval between the two visits was 6.0 months (SD ±0.5 months). The FAS (mean difference -1.4, 95% confidence interval (CI) -2.2--0.6, p = 0.001) and IS (mean difference -2.8, 95%CI -5.0--0.5, p = 0.018) of the UHDRS and the CDS (mean difference -3.2, 95%CI -5.9--0.5, p = 0.022) declined significantly during six months' follow-up. The motor (mean difference 1.9, 95%CI 0.2-3.8, p = 0.028) and cognitive score (mean difference -8.7, 95%CI -16.8--0.7, p = 0.034) of the UHDRS-FAP also deteriorated over time, in contrast to the motor and cognitive score of the UHDRS which did not show change. Concerning the cognitive domains of both scales, only the Stroop word reading component declined significantly during follow-up (mean difference -4.7, 95%CI -8.3--1.2, p = 0.011). The responsiveness analysis, including ES and SRM, is presented in Table 2. The ES and SRM were mostly small, except for the SRM of the FAS, which was moderate (-0.67).

Table 1. Demographic data of the participants at baseline

	All HD patients (n = 40)	HD patients who participated twice (n = 29)
Age, years	54.5 (±12.8)	53.8 (±13.2)
Male/female (%male)	14/26 (35.0%)	9/20 (31.0%)
CAG repeat length	44.8 (±3.8)[a]	44.4 (±3.6)
Educational level, years	13.3 (±2.9)	13.6 (±3.0)
Age of disease onset, years	40.7 (±11.3)	40.7 (±11.4)
Disease duration, years	13.4 (±5.1)	12.7 (±4.9)

Data are mean (± standard deviation), except for gender (number, %).

CAG, cytosine-adenine-guanine; HD, Huntington's disease.

[a] CAG repeat length was missing for two patients; they tested positive for HD through linkage analysis.

Table 2. Clinical characteristics of the participants at baseline and follow-up

		Baseline (n = 29)	Follow-up (n = 29)	Mean difference (95%CI)	*p*-value	ES	SRM
UHDRS	Motor score	57.8 (±25.3)	59.3 (±24.8)	1.5 (-1.5-4.6)	0.318	0.06	0.19
	Cognitive score	92.8 (±63.7)	86.2 (±72.2)	-6.6 (-14.7-1.6)	0.109	-0.10	-0.31
	Behavioral score	15.4 (±9.6)	14.3 (±10.0)	-1.1 (-3.7-1.5)	0.397	-0.11	-0.16
	Total Functional Capacity	3.1 (±2.3)	2.9 (±2.1)	-0.2 (-0.6-0.1)	0.165	-0.09	-0.22
	Functional Assessment Scale	11.2 (±6.1)	9.8 (±6.1)	-1.4 (-2.2--0.6)	**0.001**	-0.23	-0.67
	Independence Scale	59.8 (±14.4)	57.1 (±15.4)	-2.8 (-5.0--0.5)	**0.018**	-0.19	-0.47
UHDRS-FAP	Motor score	11.5 (±9.4)	13.3 (±10.2)	1.9 (0.2-3.8)	**0.028**	0.20	0.43
	Cognitive score	127.5 (±60.8)	118.8 (±69.3)	-8.7 (-16.8--0.7)	**0.034**	-0.14	-0.41
	Somatic score	5.7 (±4.9)	6.2 (±5.1)	0.5 (-0.9-1.9)	0.462	0.10	0.14
	Behavioral score	1.8 (±1.4)	2.1 (±1.4)	0.3 (-0.2-0.8)	0.231	0.21	0.21
CDS		53.4 (±13.8)	50.2 (±14.6)	-3.2 (-5.9--0.5)	**0.022**	-0.23	-0.45

Mean scores (±SD) are given for all sections of the UHDRS, UHDRS-FAP and CDS at baseline and follow-up six months later. Mean difference (95%CI) between the two assessments are shown. *p*-values were calculated using paired t-tests. Significant differences ($p<0.05$) are shown in bold.

CDS, Care Dependency Scale ; CI, confidence interval; ES, effect size; SRM, standardized response mean; UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients.

Table 3. Longitudinal data of the participants categorized by TFC stage

		TFC stages 2-3 (n = 19)		TFC stages 4-5 (n = 10)	
		Mean difference (95%CI)	*p*-value	Mean difference (95%CI)	*p*-value
UHDRS	Motor score	2.1 (-1.6-5.8)	0.251	0.4 (-5.9-6.7)	0.441
	Cognitive score	-1.6 (-11.5-8.3)	0.825	-16.0 (-30.6--1.4)	**0.012**
	Behavioral score	1.3 (-1.9-4.4)	0.409	-5.6 (-9.4--1.8)	**0.015**
UHDRS-FAP	Motor score	1.6 (-0.3-3.6)	0.102	2.4 (-1.4-6.2)	0.138
	Cognitive score	-4.3 (-13.2-4.6)	0.344	-17.2 (-34.4-0.1)	**0.047**
	Somatic score	-0.2 (-1.6-1.3)	0.728	1.8 (-1.7-5.3)	0.437
	Behavioral score	0.9 (0.5-1.4)	**0.002**	-0.9 (-1.8-0.0)	**0.047**
CDS		-3.4 (-7.0-0.1)	0.064	-2.8 (-7.8-2.2)	0.673

Mean differences (95% CI) between baseline and follow-up six months later are shown. The participants are categorized by TFC stage. *p*-values were calculated using Wilcoxon signed-rank tests. Significant differences ($p<0.05$) are shown in bold.

CDS, Care Dependency Scale; CI, confidence interval; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients.

Table 3 shows the mean differences of the UHDRS, UHDRS-FAP and CDS sections between the two time points for the different TFC stages. For HD patients in TFC stages 2-3 (middle stage) only the behavioral score of the UHDRS-FAP worsened significantly over time (mean difference 0.9, 95%CI 0.5-1.4, $p = 0.002$). For patients in TFC stages 4-5 (late stage) the cognitive score of both the UHDRS (mean difference -16.0, 95%CI -30.6--1.4, $p = 0.021$) and UHDRS-FAP (mean difference -17.2, 95%CI -34.4-0.1, $p = 0.047$) declined significantly and, interestingly, the behavioral score of both rating scales improved (UHDRS, mean difference -5.6, 95%CI -9.4--1.8, $p = 0.015$; UHDRS-FAP, mean difference -0.9, 95%CI -1.8-0.0, $p = 0.047$).

Discussion

In this study, 29 advanced HD patients who received day-care or resided in a long-term care facility were examined longitudinally. Our results showed that the motor and cognitive score of the UHDRS-FAP deteriorated during six months' follow-up, whilst the motor and cognitive score of the UHDRS did not show change. This finding suggests that

these sections of the UHDRS-FAP can detect disease progression in late stage HD, contrary to the same sections of the UHDRS, which is probably caused by the ceiling and floor effects of the UHDRS. Therefore, the UHDRS-FAP motor and cognitive domains seem more suitable for optimizing care for patients with late stage HD, especially in nursing homes. The lack of change on the UHDRS domains could be due to the fact that medication was changed in some patients; however, the UHDRS-FAP domains did deteriorate. The UHDRS-FAP motor score can be used to monitor change over time and to evaluate the effect of medication or therapy (physiotherapy, speech therapy, occupational therapy) in advanced HD, which is useful in clinical care but can also be used for research purposes. In addition, administration of this domain is minimally demanding as it only takes a few minutes. Youssov et al.[10] detected motor and cognitive deterioration over time in patients with late stage HD with both the UHDRS-FAP and UHDRS, but the slope was steeper with the UHDRS-FAP, also suggesting that disease progression in advanced HD is better detected by the UHDRS-FAP than the UHDRS. Previous studies have shown decline in motor and cognitive performance on the UHDRS, but these studies were not performed in late stage HD.[3-6] A different longitudinal study on all UHDRS cognitive tasks demonstrated deterioration through all consecutive TFC stages except from TFC stage 4 to 5, confirming the floor effect of the UHDRS cognitive section in advanced HD.[9] The same study showed that the Stroop word reading test declined most rapidly over time from premanifest HD to TFC stage 5. This item, which is part of both the UHDRS-FAP and UHDRS, was also the only cognitive task that worsened in our cohort of patients with late stage HD and therefore supports the use of the Stroop word reading test for detecting disease progression.

Of the three functional UHDRS subsections, the FAS and IS declined significantly during six months' follow-up in our cohort of advanced HD patients; the TFC did not. Decline of FAS and IS scores are in line with previous longitudinal studies.[3-5] However, these studies also reported decline of the TFC score. The reason for this discrepancy is probably the fact that their patients were in a less advanced stage of HD than our patients, since TFC scores deteriorate less rapidly in late stage HD (TFC stages 4 and 5) due to floor effects of the scale.[8] Over six months' time, the CDS also worsened significantly. Other studies in long-term care facilities have shown that the CDS declined in patients with dementia, and to a lesser extent in patients without dementia.[16,17] Our results indicate that the FAS, IS and CDS can be implemented in nursing home care to detect disease progression and individual problems in patients with late stage HD.

Instead of only determining the statistically significant differences over time, these differences were also quantified with a responsiveness analysis. This analysis showed that the ES and SRM of the UHDRS and UHDRS-FAP domains, and the CDS were mostly small, except for the SRM of the FAS which was moderate. However, small values were expected

since the follow-up time was short and therefore the mean differences of the scores between the visits small. Probably, a longer follow-up time will lead to higher ES and SRM.

The behavioral score of the UHDRS and UHDRS-FAP significantly improved after six months' follow-up in HD patients in TFC stages 4 and 5. These results suggest that psychiatric symptoms in advanced HD patients fade away as disease duration progresses. However, previous longitudinal behavioral assessment in late stage HD did not show change on the UHDRS and UHDRS-FAP.[10] Other studies have demonstrated that apathy increased as disease duration and TFC stage progressed[18-20], whereas depression was more common in the mild-to-moderate disease severity stages.[20,21] Depression and anxiety may diminish in later stages of the disease as emotions decrease and insight lessens, explaining our results. However, it is important to note that of the 11 HD patients who were lost to follow-up, 10 patients were in TFC stages 4 and 5. So, nearly all dropout occurred in the most advanced stages, which may have caused bias.

A strength of our study is the administration of the UHDRS and UHDRS-FAP on the same day, so day-to-day variation of patients' symptoms was excluded. In general, longitudinal research is challenging in nursing homes, because patients are in the last phase of their lives and chance of dropout is high. This is especially difficult for rare diseases, like HD. Due to the high number of patients who were lost to follow-up our sample size was small, which is a limitation of our study. The short follow-up time of six months is also a limitation. Ideally, the assessments are repeated after 12, 18 and 24 months in order to examine how the scores of the rating scales evolve over a longer period of time. Another limitation is the administration of the rating scales by two raters, which may have influenced the results due to interrater reliability. Furthermore, not all caregivers were present at the study visits, which may have led to underreporting of symptoms by the patient due to reduced insight.

In conclusion, our longitudinal study in patients with advanced HD in a long-term care facility showed that the motor and cognitive score of the UHDRS-FAP, the FAS and IS of the UHDRS, and the CDS deteriorated during six months' follow-up. This finding suggests that these sections can detect disease progression in late stage HD. Therefore, these scores are recommended for use in nursing homes to optimize HD care by monitoring disease progression and by evaluating the effect of interventions in clinical care. The behavioral score significantly improved with both rating scales in patients in TFC stage 4-5, indicating that psychiatric symptoms fade away as the disease progresses.

References

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

2. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

3. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

4. Siesling S, Van Vugt JPP, Zwinderman KAH, Kieburtz K, Roos RAC. Unified Huntington's Disease Rating Scale: a follow up. Mov Disord 1998; 13: 915–919.

5. Meyer C, Landwehrmeyer B, Schwenke C, Doble A, Orth M, Ludolph AC. Rate of change in early Huntington's disease: a clinicometric analysis. Mov Disord 2012; 27: 118–124.

6. Toh EA, MacAskill MR, Dalrymple-Alford JC, Myall DJ, Livingston L, Macleod SAD, et al. Comparison of cognitive and UHDRS measures in monitoring disease progression in Huntington's disease: a 12-month longitudinal study. Transl Neurodegener 2014; 3: 15.

7. Feigin A, Kieburtz K, Bordwell K, Como P, Steinberg K, Sotack J, et al. Functional decline in Huntington's disease. Mov Disord 1995; 10: 211–214.

8. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

9. Baake V, Reijntjes RHAM, Dumas EM, Thompson JC, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017; 95: 51–62.

10. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

11. Winder JY, Achterberg WP, Marinus J, Gardiner SL, Roos RAC. Assessment scales for patients with advanced Huntington's disease: comparison of the UHDRS and UHDRS-FAP. Mov Disord Clin Pract 2018; 5: 527–533.

12. Dijkstra A, Buist G, Moorer P, Dassen T. Construct validity of the Nursing Care Dependency Scale. J Clin Nurs 1999; 8: 380–388.

13. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

14. Agniel A, Joanette Y, Doyon B, Duchein C. Protocole Montreal-Toulouse d'Evaluation des Gnosies Visuelles. Fr L'Ortho Ed, 1992.

15. Cohen J. Statistical power analysis for the behavioral sciences. New York: Acad Press, 1977.

16. Dijkstra A, Sipsma D, Dassen T. Predictors of care dependency in Alzheimer's disease after a two-year period. Int J Nurs Stud 1999; 36: 487–495.

17. Schüssler S, Lohrmann C. Change in care dependency and nursing care problems in nursing home residents with and without dementia: a 2-year panel study. PLoS One 2015; 10: 1–12.

18. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 219–226.

19. Kingma EM, Van Duijn E, Timman R, Van der Mast RC, Roos RAC. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008; 30: 155–161.

20. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci 2012; 24: 53–60.

21. Paulsen JS, Nehl C, Ferneyhough Hoth K, Kanz JE, Benjamin M, Conybeare R, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci 2005; 17: 496–502.

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CHAPTER 6

Marriage as protector for nursing home admission in Huntington's disease

Abstract

Background: Huntington's disease is a progressive, incurable neurodegenerative disorder and it is not possible to delay onset or progression of the disease. Consequently, the disease leads to functional decline and loss of independency and finally to institutionalization.

Objective: The aim of this study is to identify factors which are associated with nursing home admission in patients with Huntington's disease.

Methods: The Unified Huntington's Disease Rating Scale (UHDRS) and the UHDRS-For Advanced Patients (UHDRS-FAP) were administered in 28 nursing home residents and 12 patients receiving day-care. Comparisons between the two groups were performed using Mann-Whitney U tests and Chi-square tests. The significantly different findings were fitted in individual univariate logistic regression models to determine which components were most predictive of institutionalization.

Results: Day-care participants were more often married than nursing home residents (p = 0.006) and were functionally more independent: the Functional Assessment Scale (p = 0.022) of the UHDRS was significantly higher. Not being married was more predictive for nursing home admission than functional capacity in the regression models.

Conclusions: Our results suggest that being married is protective for nursing home placement. Possibly, a caregiver living with a patient can assist with activities of daily living which the patient could not have done independently, resulting in being able to live at home longer. Providing support to unmarried patients, who do not have a caregiver living with them, by home care services specialized in Huntington's disease might increase the chance of the best possible care before institutionalization and postpone nursing home admission.

Introduction

Huntington's disease (HD) is a hereditary, progressive neurodegenerative disorder caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene on chromosome 4.[1] The disease is clinically characterized by a triad of motor, cognitive, and psychiatric symptoms. These symptoms ultimately lead to functional decline and loss of independency as HD progresses into a more advanced stage. The mean age at disease onset is 30-50 years, with a mean disease duration of 17-20 years.[2] HD is presently incurable and it is not possible to delay either onset or progression of the disease. Due to the progressive nature of the disease, it eventually becomes more difficult for care to be provided at home, which leads to admission in a nursing home. However, guidelines for management and care of advanced HD patients in long-term care facilities are limited and only discuss different views on nursing home placement and treatment.[3]

Demographically HD patients in nursing home facilities are younger (45-59 years)[4-7] than the average nursing home resident (83-85 years)[8,9], and therefore the need for care is different. Previous studies have shown that motor dysfunction, impaired activities of daily living (ADL), and reduced scores on the Mini-Mental State Examination (MMSE) were predictors of institutionalization in HD.[5,6] Psychiatric symptoms did not predict nursing home placement. However, these studies were conducted retrospectively and only one study[5] used the Unified Huntington's Disease Rating Scale (UHDRS), which is most commonly used for the clinical assessment of symptoms and signs in HD.[10]

Identification of predictors for institutionalization may lead to interventions and treatment strategies that can postpone the need for nursing home placement. Additionally, characterization of HD specific problems in nursing home residents could optimize their care. Therefore, the aim of this present study is to examine the differences between nursing home residents and day-care participants with HD, using the UHDRS and UHDRS-For Advanced Patients (UHDRS-FAP), which is developed for patients with late stage HD.[11] We hypothesize that both nursing home residents as well as day-care participants are in an advanced stage of HD, and therefore we aim to examine which factors are associated with institutionalization.

Materials and methods

Setting and participants

Our study was carried out at the Huntington Center Topaz Overduin (Katwijk, the Netherlands), which is a nursing home with 70 residents, 20 day-care patients, and over 100 outpatients, specialized in the care for HD patients, both in late and early stages. Specialized medical doctors, therapists, psychologists, and nurses provide long-term care and day-care, organize activities, and offer support for patients (and their family) who live at home. The long-term care facility comprises three departments: one department is specialized in psychiatric problems, one department provides care for patients highly dependent on care, and one department provides care for patients less dependent on care. Institutionalized patients and patients receiving day-care, with a clinically and/or genetically confirmed diagnosis of HD, were asked to participate in this study. The local medical ethics committee approved the study and written informed consent was obtained from all participants or their caregivers. Assessments performed in this study include the UHDRS, followed by the UHDRS-FAP on the same day. The scales were administered by two medical doctors experienced with HD. They interviewed and examined the patients, preferably in the presence of their caregiver.

Assessments

The UHDRS consists of four domains, which are motor function, cognitive function, behavioral abnormalities, and functional capacity.[10] The motor section comprises 31 items assessing chorea, dystonia, eye movements, bradykinesia/rigidity, and gait/balance.[10] All items are rated on a 0 to 4 point scale with 4 indicating the most severe impairment. The range of the Total Motor Score (TMS) is 0-124, with higher scores indicating more motor disturbances. The cognitive domain consists of the Verbal Fluency test[12], the Symbol Digit Modalities test[13], and the Stroop test (color naming, word reading, and interference).[14] Higher scores indicate better cognitive performance. The behavioral component assesses the frequency and severity of 11 items, such as depression, anxiety, irritability, apathy, and other behavioral symptoms.[10] The items are rated from 0 to 4 and the total score ranges from 0 to 88, with higher scores indicating more severe psychiatric abnormalities. The functional domain is composed of three subunits[10]: the Functional Assessment Scale (FAS) including 25 yes/no questions about common daily tasks (range 0-25), the Independence Scale (IS) measuring the level of independence with one single score (range 10-100), and the Total Functional Capacity (TFC) assessing occupation, finances, domestic

chores, ADL, and care level (range 0-13).[15] Overall, higher functional scores indicate better function.

The UHDRS-FAP is divided into four sections: motor, cognitive, somatic, and behavior.[11] Motor performance is measured by 14 items, such as walking around, capacity to transfer, eat, and wash independently, dysphagia, imitation synkinesias, and other motor components (range 0-52). The cognitive score includes functional and categorical matching of the Protocole Toulouse Montreal d'Evaluation des Gnosies Visuelles (PEGV)[16], pointing, simple commands, the Stroop test, orientation, participation in activities, imitation (apraxia), and automatic series. The somatic domain comprises 10 items assessing hyperhidrosis, hypersalivation, incontinence, digestion, hypersomnia, and pressure ulcers (range 0-28). The behavioral subscale includes 8 yes/no questions about the presence of psychiatric abnormalities (range 0-8). Higher scores on the motor, somatic, and behavioral sections indicate more impairment, while higher scores on the cognitive domain indicate better performance.

Statistical analysis

Demographic differences between nursing home residents and day-care participants with HD were analysed using Mann-Whitney U tests or Chi-square tests. Median scores of each section of the UHDRS and UHDRS-FAP were calculated for the institutionalized patients and the patients receiving day-care. We also calculated a modified TFC without the care level-item, because this item automatically distinguishes between patients who are admitted to a long-term care facility and patients who receive day-care. Comparisons of the scores between the two groups were performed with Mann-Whitney U tests. For the scores of the UHDRS and UHDRS-FAP sections that were significantly different between nursing home residents and day-care participants, we calculated the frequencies of the items within the domain. The significantly different findings between the two groups were fitted in individual univariate logistic regression models to determine which components were most predictive of institutionalization. In order to compare the outcomes of the univariate regression models the scores were dichotomized at the median in high and low scores. A p-value of <0.05 was considered statistically significant. Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 23.

Results

Forty HD patients participated in our study, including 28 nursing home residents and 12 day-care participants. Of the 28 nursing home residents, 12 came from the 21-bed low-care unit (57%), 9 from the 29-bed high-care unit (31%), and 7 from the 20-bed psychiatry unit (35%). Twelve of the 20 day-care patients chose to participate (60%). Demographic data of the nursing home residents and day-care participants are shown in Table 1. Day-care participants were more often married or had a domestic partnership than nursing home residents (p = 0.006). Marital status changed for three residents during admission, but was also significantly different between day-care participants and residents at the time of admission (p = 0.038). Other demographics, such as age and disease duration, were not significantly different between the two groups. Age and gender of study participants were similar to the age and gender of the patients who did not consent to participate in the study. Likewise, only 15 of all 70 nursing home patients were married (21.4%) compared to 14 of 20 day-care patients (70.0%) (p < 0.001).

Table 1. Demographics for nursing home residents and day-care participants with Huntington's disease

	Nursing home residents (n = 28)	Day-care participants (n = 12)	*p*-value
Age, years	57.5 (46.0-66.8)	51.5 (45.3-63.8)	0.512
Gender, male/female (%male)	8/20 (28.6%)	6/6 (50.0%)	0.193
CAG repeat length	44.0 (42.0-47.3)[a]	44.0 (42.0-47.5)	0.938
Educational level, years	12.0 (12.0-14.5)	14.5 (12.0-16.8)	0.074
Age of disease onset, years	40.0 (31.3-49.8)	40.5 (33.3-49.3)	0.998
Disease duration, years	13.0 (10.0-18.8)	11.5 (8.3-16.3)	0.202
Residence duration, years	3.0 (1.3-5.0)	NA	NA
Medication for HD, yes/no (%yes)	26/2 (92.9%)	12/0 (100.0%)	0.342
Married, yes/no (%yes)	8/20 (28.6%)	9/3 (75.0%)	**0.006**

Data are median (IQ-range); except for gender, medication for HD, and married, which are number (%). *p*-values were calculated using Mann-Whitney U tests; except for gender, medication for HD, and married, which were calculated using Chi-square tests.

[a] CAG repeat length was missing for two nursing home residents; they tested positive for HD through linkage analysis.

CAG, cytosine-adenine-guanine; HD, Huntington's disease; NA, not applicable; IQ, interquartile.

The median scores of the UHDRS and UHDRS-FAP sections for the institutionalized patients and patients receiving day-care are given in Table 2. The FAS (p = 0.022) and TFC (p = 0.011) of the UHDRS functional domain were significantly lower for nursing home residents compared to day-care participants, indicating a worse function. However, the modified TFC did not show a significant difference (p = 0.163). The scores of the other UHDRS sections and all UHDRS-FAP sections did not show any differences between the two groups.

Figure 1 shows how many patients were able to perform the common daily tasks of the FAS independently, demonstrating that particularly number 13 (take own medications without help), 18 (walk to places in neighborhood without help), and 24 (use toilet/commode without help) were less frequently performed independently by nursing home residents. The logistic regression model with married/domestic partnership as independent variable showed that not being married (i.e. not having a partner) was predictive of institutionalization in patients with HD (p = 0.010, OR 7.50, 95%CI 1.60-35.08), meaning that non-married patients were 7.50 times more likely to being

Table 2. Clinical characteristics of nursing home residents and day-care participants with Huntington's disease

		Nursing home residents (n = 28)	Day-care participants (n = 12)	p-value
UHDRS	Motor score	75.0 (40.5-88.0)	49.0 (29.8-82.3)	0.115
	Cognitive score	51.5 (10.0-96.8)	102.0 (51.5-148.8)	0.069
	Behavioral score	12.5 (8.0-24.8)	17.0 (9.0-25.0)	0.610
	Functional Assessment Scale	7.5 (1.3-13.8)	13.5 (8.3-17.0)	**0.022**
	Independence Scale	60.0 (36.3-65.0)	62.5 (52.5-70.0)	0.163
	Total Functional Capacity	1.0 (0.0-3.8)	3.5 (2.3-6.8)	**0.011**
	Modified TFC	1.0 (0.0-3.8)	2.5 (1.3-5.8)	0.163
UHDRS-FAP	Motor score	13.0 (4.3-25.3)	8.0 (6.0-17.8)	0.512
	Cognitive score	89.8 (51.8-139.9)	141.0 (90.3-167.5)	0.096
	Somatic score	5.0 (1.3-13.0)	5.5 (2.3-9.0)	0.805
	Behavioral score	2.0 (1.0-3.0)	1.0 (0.3-3.0)	0.531

Data are median (IQ-range). p-values were calculated using Mann-Whitney U tests.
UHDRS, Unified Huntington's Disease Rating Scale; UHDRS-FAP, Unified Huntington's Disease Rating Scale-For Advanced Patients; TFC, Total Functional Capacity; IQ, interquartile.

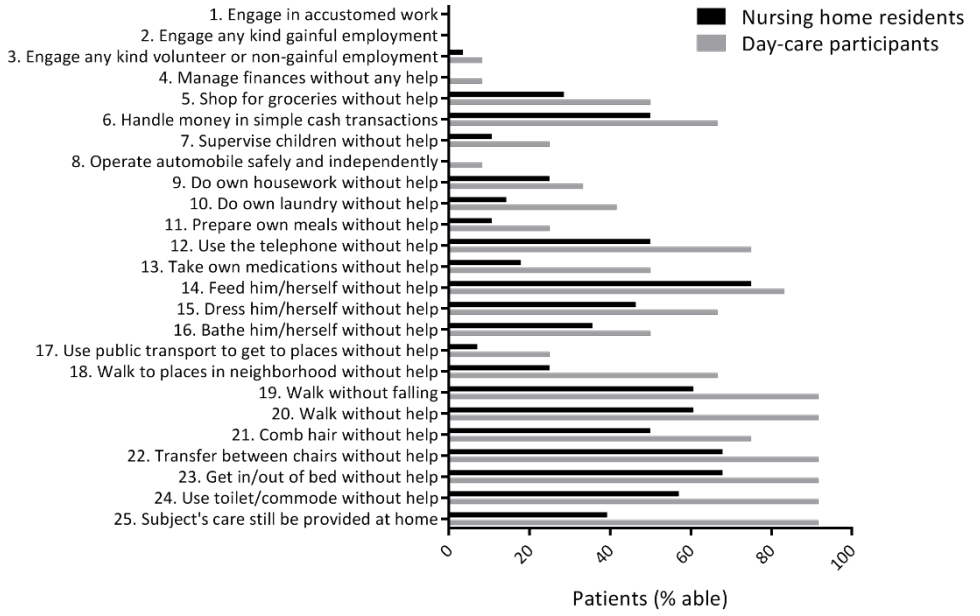

Figure 1. Percentage of nursing home residents and day-care participants being able to perform the common daily tasks of the Functional Assessment Scale independently.

institutionalized than married patients. The univariate regression model with the dichotomized FAS score as independent variable showed that lower scores were also associated with institutionalization (p = 0.047, OR 4.64, 95%CI 1.02-21.00), but this association is not as strong as the association between not being married and nursing home admission.

Discussion

This study identified associations between clinical characteristics of patients with advanced HD in day-care and in a nursing home. Our results showed that lower scores on the FAS of the UHDRS functional domain and not being married were related to institutionalization. Probably, lower functional capacity causes more dependency on care for common daily tasks, which ultimately leads to institutionalization. The association between lower functional capacity and nursing home placement is consistent with previous findings that the ADL scale is related to institutionalization.[6] We did not find

correlations between institutionalization and motor disturbances, cognitive performance, and behavioral abnormalities on the UHDRS and UHDRS-FAP. This finding indicates that nursing home residents are not more affected by the triad of symptoms characteristic for HD then patients in day-care, suggesting that these symptoms do not cause institutionalization. Our findings contrast with the results of previous studies, which indicated bradykinesia, impaired gait, and impaired tandem walking of the UHDRS-TMS[5], the Motor Impairment Score (MIS), and the MMSE[6] as predictors for nursing home placement. Like our study, psychiatric symptoms were not shown to predict institutionalization in HD in these studies.[5,6] However, in our study less patients from the nursing home department specialized in psychiatric problems chose to participate compared to the other departments, which may have underestimated the amount of psychiatric symptoms in the nursing home residents.

The results of the individual univariate logistic regression analysis suggest that not being married is more predictive of institutionalization in HD patients than lower scores on the FAS. This finding implies that having a partner protects better against nursing home admission than higher functional ability. Possibly, a caregiver living with a patient assists with ADL tasks which the patient could not have done independently, resulting in being able to live at home longer than a patient without a caregiver living with the patient. Assistance with ADL tasks and care can also be provided by home care services or caregivers not living with a patient (usually their children), but this care is not available 24 hours a day. For example, when a patient is not able to use the toilet independently or walk to places in the neighborhood independently (with the chance of wandering), (s)he usually needs supervision 24 hours a day by a partner or nursing home facility. HD patients are usually admitted to a nursing home when middle-aged.[4-7] Accordingly, partners of HD patients are generally younger than partners of average nursing home residents. Younger partners may have a better health status than older partners and may, therefore, be better capable to provide care for the patient at home. However, younger partners usually have a job and, consequently, are often not home to take care of the patient.

To our knowledge, no study has been performed investigating the influence of a partner/caregiver on institutionalization in HD. A systematic review in patients with dementia showed that married patients and patients living with their caregiver had a lower risk of nursing home placement.[17] Greater dementia severity, older age, neuropsychiatric symptoms, impaired cognition, and more functional impairment were also predictors of long-term care admission.[17,18] Additionally, caregiver burden and inability of the caregiver to care for the patient were stated as reasons for institutionalization by caregivers of patients with dementia. The reasons for admission varied between countries. For example, none of the French caregivers expressed inability to care as a reason for institutionalization in patients with dementia, while this category

was mentioned by 30% of the Spanish caregivers.[18] Reasons for nursing home placement in HD could also differ between countries, due to the organization of nursing home care, financial costs, and cultural aspects. Therefore, our results may be hard to apply to other countries, where HD care is less well organized or more expensive than in the Netherlands.

Ideally, identification of predictors for institutionalization lead to interventions and treatment strategies that postpone the need for nursing home placement. However, not having a partner cannot be changed. Providing support to unmarried HD patients, who do not have a caregiver living with them, by home care services specialized in HD might increase the chance of the best possible care in the own environment before institutionalization and postpone nursing home admission. The last question of the FAS is 'could subject's care still be provided at home?', which gives an overview of the examiner's perception of the patient's functional ability. The examiners answered this question with 'yes' in 39.3% of the institutionalized HD patients, suggesting that for almost 40% of the institutionalized patients care could be provided at home if the patient had a suitable caregiver/partner. After nursing home placement, the FAS can provide information about a patient's dependency on care easily and quickly, which could possibly optimize their care. For example, less than 50% of the nursing home residents were able to bath or dress themselves without help, but more than 50% of the patients were able to walk, use the toilet, or feed themselves without help.

The strength of our study is the use of the UHDRS and UHDRS-FAP for the clinical assessment of the patients. These scales were developed especially for HD patients. A limitation of our study is the small sample size and, therefore, this study might be underpowered. Due to the small sample size, we could not perform a multivariate regression analysis and in the univariate regression models the ranges of the confidence intervals of the odds ratios were very wide. The use of two examiners is another limitation and could have influenced our results due to interrater reliability. For some patients the caregiver could not attend the visit, which may have caused underreporting of symptoms due to reduced awareness of symptoms by the patient. Additionally, we did not collect information about the caregivers or questioned the caregivers independently from the patients. Further research is needed to investigate the role of caregivers. Ideally, cultural aspects, financial costs, and organization of HD care across different countries will also be explored.

In conclusion, our study in patients with advanced HD residing in a nursing home or receiving day-care showed that not being married/not having a partner and low functional abilities were associated with institutionalization. Motor impairment, cognitive function, and psychiatric symptoms were not related to nursing home placement. Marital status

seemed more predictive for nursing home admission than functional capacity, suggesting that a partner can compensate for high dependency on care for ADL tasks.

References

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–983.

2. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40.

3. Simpson SA. Late stage care in Huntington's disease. Brain Res Bull 2007; 72: 179–181.

4. Nance MA, Sanders G. Characteristics of individuals with Huntington disease in long-term care. Mov Disord 1996; 11: 542–548.

5. Wheelock VL, Tempkin T, Marder K, Nance M, Myers RH, Zhao H, et al. Predictors of nursing home placement in Huntington disease. Neurology 2003; 60: 998–1001.

6. Rosenblatt A, Kumar BV, Margolis RL, Welsh CS, Ross CA. Factors contributing to institutionalization in patients with Huntington's disease. Mov Disord 2011; 26: 1711–1716.

7. Zarowitz BJ, O'Shea T, Nance M. Clinical, demographic, and pharmacologic features of nursing home residents with Huntington's disease. J Am Med Dir Assoc 2014; 15: 423–428.

8. Hemmingsson E-S, Gustafsson M, Isaksson U, Karlsson S, Gustafson Y, Sandman P-O, et al. Prevalence of pain and pharmacological pain treatment among old people in nursing homes in 2007 and 2013. Eur J Clin Pharmacol 2018; 74: 483–488.

9. Ivanova I, Wauters M, Van der Stichele R, Christiaens T, De Wolf J, Dilles T, et al. Medication use in a cohort of newly admitted nursing home residents (Ageing@NH) in relation to evolving physical and mental health. Arch Gerontol Geriatr 2018; 75: 202–208.

10. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

11. Youssov K, Dolbeau G, Maison P, Boissé MF, Cleret de Langavant L, Roos RA, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

12. Benton AL, Hamsher K DeS. Multilingual aphasia examination manual. Iowa City: Univ Iowa, 1978.

13. Smith A. Symbol digit modalities test manual. Los Angeles: West Psychol Serv, 1973.

14. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643–662.

15. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

16. Agniel A, Joanette Y, Doyon B, Duchein C. Protocole Montreal-Toulouse d'Evaluation des Gnosies Visuelles. Fr L'Ortho Ed, 1992.

17. Cepoiu-Martin M, Tam-Tham H, Patten S, Maxwell CJ, Hogan DB. Predictors of long-term care placement in persons with dementia: a systematic review and meta-analysis. Int J Geriatr Psychiatry 2016; 31: 1151–1171.

18. Afram B, Stephan A, Verbeek H, Bleijlevens MHC, Suhonen R, Sutcliffe C, et al. Reasons for institutionalization of people with dementia: informal caregiver reports from 8 European countries. J Am Med Dir Assoc 2014; 15: 108–116.

CHAPTER 7

Discussion and conclusions

Focus of this thesis

In Huntington's disease (HD), detecting the course of motor, cognitive, and psychiatric symptoms is of great importance. If the presence, severity, and progression of symptoms and signs can be detected, the effect of therapeutic interventions can be monitored, which is useful in HD research and in clinical care. However, to measure change of symptoms and signs accurately, reliable and valid assessment scales are necessary. For the detection and monitoring of clinical features different rating scales are used, since the symptoms and signs of HD change as the disease progresses from premanifest stage to advanced stage. Therefore, the main aim of this thesis was to investigate the measurement properties of the Unified Huntington's Disease Rating Scale (UHDRS)[1] and of the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP)[2] in various severity stages of HD and to give recommendations on which items or sections of the scales are, or are not, useful in which stage of the disease.

Assessment of motor symptoms

The clinical assessment of motor symptoms in HD is usually performed with the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). The developers of the scale found a good interrater reliability, with an intraclass correlation coefficient (ICC) of 0.94.[1] Our study in a large cohort of raters, who participated in the annual online certification of the UHDRS-TMS, also showed a good, but lower, interrater reliability of the UHDRS-TMS (ICC = 0.847) (**chapter 2**). The lower interrater reliability in our study can more than likely be explained by the fact that the raters involved in our study had variable levels of experience, and were not all HD experts. Interestingly, we found a poor interrater reliability for all five dystonia items of the UHDRS-TMS (ICC < 0.400), suggesting that the rating of these items is difficult to interpret, probably as a consequence of the subjective nature of the response options (absent, slight, mild, moderate, or marked dystonia). Therefore, removing, changing, or combining some of the dystonia items, or providing clearer response options should be explored, as poor interrater reliability hampers the monitoring of progression of HD motor symptoms. A previous study on the internal consistency of the UHDRS-TMS showed that after elimination of all dystonia items the internal consistency hardly changed, thereby also questioning the importance of the dystonia items.[3] We believe that the dystonia items can be omitted in patients with mild to moderate HD, and should only be examined in patients with advanced HD, as dystonia often arises as the disease progresses. The annual online certification of the UHDRS-TMS also showed that the percentage of motor items scored correctly dropped significantly between baseline and follow-up (from 87.8% to 86.4%). However, a decrease of 1.4%

seems only marginally relevant. We recommend that raters should watch the teaching video of the UHDRS-TMS before each certification to be reminded of the established standards. The online video system allowed us to examine the interrater reliability of the UHDRS-TMS for a large number of raters. However, the use of video recordings was also a limitation of our study, since the raters did not perform an actual physical examination themselves and in real life the clinical presentation of a patient usually varies.

For the measurement of reliability, various parameters can be used, such as ICC, Cohen's kappa, and percentage agreement. We did not use percentage agreement, because this parameter does not take chance agreement into account. A weighted kappa can be used for categorical variables, such as the items of the UHDRS-TMS. The rationale for a weighted kappa is that misclassifications between adjacent categories are less serious than those between more distant categories. However, given that calculating a weighted kappa is cumbersome and complicated, especially if multiple raters are involved, we used the ICC, because the ICC is equivalent to a weighted kappa if a quadratic weighting scheme is used.[4,5]

Clinical diagnosis of HD is generally based on the appearance of motor symptoms. Therefore, the UHDRS-TMS is often used in HD gene carriers to distinguish between premanifest individuals and manifest patients for research purposes. However, oculomotor abnormalities have already been observed with eye-tracking equipment before disease onset.[6-9] Our study in premanifest HD gene carriers and healthy controls showed that horizontal ocular pursuit was the only affected item of the UHDRS oculomotor domain in premanifest individuals near to HD onset compared to controls (**chapter 3**). This finding suggests that horizontal ocular pursuit can be used to detect early clinical signs of HD in individuals who are at risk for developing HD in a much easier way than eye-tracking equipment. The fact that the other oculomotor items of the UHDRS-TMS did not show any differences between premanifest individuals and controls does not necessarily mean that they are not present, but more likely implies that these items are not sensitive enough to detect oculomotor abnormalities in premanifest HD gene carriers.

Apart from the UHDRS-TMS, other studies have focussed on more quantitative instruments to measure motor impairment, such as eye-tracking equipment, tongue force analysis, and quantitative-motor (Q-Motor) assessments.[6,10,11] Research has shown that Q-Motor measures were more sensitive than the UHDRS-TMS and exhibited no placebo effect.[12] While these objective instruments are useful for research purposes, in clinical practice the UHDRS-TMS seems a more feasible assessment.

Assessment of patients with advanced HD

Severity of HD is usually classified into five stages using the Total Functional Capacity (TFC) subscale of the UHDRS: stage 1 (TFC 11-13), stage 2 (TFC 7-10), stage 3 (TFC 3-6), stage 4 (TFC 1-2), and stage 5 (TFC 0).[13] In patients with advanced HD (TFC stages 4 and 5), ceiling and floor effects of the UHDRS hamper the monitoring of changes over time.[14] Therefore, the UHDRS-FAP has been developed voor late stage HD.[2] Our cross-sectional study in advanced HD patients, residing in a nursing home or receiving day-care, showed that the motor scores of the UHDRS-FAP and UHDRS were the only subscales with a significantly worse score in TFC stage 5 compared to TFC stage 4 (**chapter 4**). The range of the UHDRS-FAP motor score was broader, the standard error of measurement (SEM) was lower, and the effect size r was higher than for the UHDRS motor score, suggesting that the UHDRS-FAP motor score differentiates better between patients in the highest TFC stages than the UHDRS motor score. Therefore, this subscale can possibly improve disease monitoring and, subsequently, care in patients with late stage HD in long-term care facilities. The cognitive and behavioral domains of both scales did not differ between TFC stages 4 and 5, and do not seem useful for differentiating between patients with advanced HD. We found a high internal consistency and high interrater reliability for the motor and cognitive scores of both scales, confirming previous findings.[1,2] The interrater reliability of the UHDRS-TMS in this study (ICC = 0.876) was similar to the one in our study on the UHDRS-TMS certification (ICC = 0.847). The behavioral scores of both scales showed low-to-moderate values for internal consistency and interrater reliability. This contradicts previous studies, which found high ICC values for an adjusted version of the UHDRS behavioral section.[15,16] However, they used a 'clinically relevant' interrater reliability, which means only differences larger than one point were included.

Our longitudinal study in late stage HD showed that the motor and cognitive scores of the UHDRS-FAP deteriorated during six months follow-up, while the motor and cognitive scores of the UHDRS did not show change (**chapter 5**). Previous research in late stage HD showed that both the UHDRS-FAP and UHDRS motor and cognitive scores deteriorated over time, but the slope was steeper with the UHDRS-FAP.[2] Both studies suggest that disease progression in advanced HD is better detected by the UHDRS-FAP than the UHDRS. Therefore, we recommend the use of the UHDRS-FAP motor and cognitive scores in nursing homes to optimize HD care by monitoring disease progression and by evaluating the effect of interventions in clinical care. The Functional Assessment Scale (FAS) and Independence Scale (IS) of the UHDRS, and the Care Dependency Scale (CDS)[17] also worsened over six months' time. Other studies in long-term care facilities also found a decline of the CDS in patients with dementia, and to a lesser extent in patients without dementia.[18,19] Interestingly, the behavioral scores of the UHDRS-FAP and UHDRS improved

in HD patients in TFC stages 4 and 5, suggesting that psychiatric symptoms fade away as the disease progresses. Previous studies also showed that depression and anxiety diminish in more advanced HD as emotions decrease and insight lessens.[20,21] Decline of psychiatric symptoms could also be caused partly by less communicative abilities of patients in late stage HD. Additionally, increased motor symptoms may lead to less strength and coordination to hit something, and therefore detection of irritability and agitation could be more complicated. For these reasons, the standard behavioral assessments do not seem suitable for advanced disease stages.

In the same cohort of late stage HD patients, we also examined the demographical and clinical differences between nursing home residents and day-care patients (**chapter 6**). None of the UHDRS-FAP or UHDRS subscales showed differences between the two groups, except for the FAS. This functional scale of the UHDRS demonstrated more dependency on care for common daily tasks for the institutionalized patients compared to the day-care participants. Interestingly, the most predictive factor for nursing home admission was not being married. This finding implies that a partner can assist with common daily tasks which a patient could not have done independently, resulting in being able to live at home longer. A systematic review on patients with dementia also showed that married patients had a lower risk of nursing home placement than patients without a partner.[22] Providing support to unmarried patients and their caregivers by home care services specialized in HD might increase the chance of the best possible care in the own environment before institutionalization and postpone nursing home admission. Furthermore, individual case management by social workers specialized in HD could also contribute to better care. Limitations of our studies in patients with advanced HD were the small sample size of 40 participants and the administration of the rating scales by two raters, which may have influenced the results due to interrater reliability.

Future perspectives

The therapeutic interventions that are currently being developed and tested aim to slow down progression of HD. To measure change of clinical features accurately, reliable and valid assessment scales and measurement instruments are necessary. The UHDRS-TMS is widely used in therapeutic clinical trials and often serves as primary endpoint to assess efficacy of interventions. We showed that the UHDRS-TMS has a high interrater reliability, except for all dystonia items, which showed a poor interrater reliability. Future studies are required to explore how the dystonia items can be improved or to examine if objective motor assessments can measure dystonia more reliable than the UHDRS-TMS.

It is important to realize that sensitive assessment scales and measurement instruments differ from premanifest HD to early, moderate, and advanced HD. We demonstrated that for the identification of motor impairment in premanifest HD, horizontal ocular pursuit can be used, while the saccade initiation and saccade velocity items did not show deficits in premanifest HD. In late stage HD, however, we showed that the motor and cognitive sections of the UHDRS-FAP were more sensitive to detect changes than the motor and cognitive domains of the UHDRS. Although less interventional research is being performed in patients with advanced HD compared to patients in the early stages of the disease, the implementation of the UHDRS-FAP instead of the UHDRS in nursing homes to optimize clinical care is an important goal for the future. Additionally, the UHDRS-FAP should be investigated for a longer follow-up period.

Recently, proposals have been made for the use of measurement instruments that relate to health as the ability to adapt and to self-manage.[23] Therefore, we believe that the UHDRS-FAP should not only include sections on motor, cognitive, and behavioral symptoms, but should also assess functional status and include quality of life questionnaires. For the development of these sections, patients' and caregivers' input on what topics and questions should be included is important.

Identification of predictors for institutionalization may lead to interventions and treatment strategies that postpone the need for nursing home admission. We demonstrated that not having a partner was associated with nursing home placement in HD. However, we did not collect additional information about the partners or questioned the partners independently from the patients. Future research on the role of caregivers, cultural aspects, and financial costs may identify more predictors for institutionalization in HD. This information is of great importance since HD patients are usually younger than the average nursing home resident, and therefore the need for care and support is probably different.

References

1. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136–142.

2. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret de Langavant L, Roos RAC, et al. The Unified Huntington's Disease Rating Scale For Advanced Patients: validation and follow-up study. Mov Disord 2013; 28: 1995–2001.

3. Siesling S, Zwinderman AH, van Vugt JPP, Kieburtz K, Roos RAC. A shortened version of the motor section of the Unified Huntington's Disease Rating Scale. Mov Disord 1997; 12: 229–234.

4. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educ Psychol Meas 1973; 33: 613–619.

5. De Vet HCW, Terwee CB, Mokkink LB, Knol DL. Measurement in medicine. Cambridge: Univ Cambridge, 2011.

6. Blekher TM, Yee RD, Kirkwood SC, Hake AM, Stout JC, Weaver MR, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. Vision Res 2004; 44: 2729–2736.

7. Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, et al. Saccades in presymptomatic and early stages of Huntington disease. Neurology 2006; 67: 394–399.

8. Antoniades CA, Altham PME, Mason SL, Barker RA, Carpenter R. Saccadometry: a new tool for evaluating presymptomatic Huntington patients. Neuroreport 2007; 18: 1133–1136.

9. Hicks SL, Robert MPA, Golding CVP, Tabrizi SJ, Kennard C. Oculomotor deficits indicate the progression of Huntington's disease. Prog Brain Res 2008; 171: 555-558.

10. Reilmann R, Bohlen S, Klopstock T, Bender A, Weindl A, Saemann P, et al. Tongue force analysis assesses motor phenotype in premanifest and symptomatic Huntington's disease. Mov Disord 2010; 25: 2195–2202.

11. Reilmann R, Bohlen S, Kirsten F, Ringelstein EB, Lange HW. Assessment of involuntary choreatic movements in Huntington's disease – Toward objective and quantitative measures. Mov Disord 2011; 26: 2267–2273.

12. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. Handb Clin Neurol 2017; 144: 209–225.

13. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29: 1–3.

14. Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburtz K, et al. Rate of functional decline in Huntington's disease. Neurology 2000; 54: 452–458.

15. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 219–226.

16. Kingma EM, Van Duijn E, Timman R, Van der Mast RC, Roos RAC. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008; 30: 155–161.

17. Dijkstra A, Buist G, Moorer P, Dassen T. Construct validity of the Nursing Care Dependency Scale. J Clin Nurs 1999; 8: 380–388.

18. Dijkstra A, Sipsma D, Dassen T. Predictors of care dependency in Alzheimer's disease after a two-year period. Int J Nurs Stud 1999; 36: 487–495.

19. Schüssler S, Lohrmann C. Change in care dependency and nursing care problems in nursing home residents with and without dementia: a 2-year panel study. PLoS One 2015; 10: 1–12.

20. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci 2012; 24: 53–60.

21. Paulsen JS, Nehl C, Ferneyhough Hoth K, Kanz JE, Benjamin M, Conybeare R, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci 2005; 17: 496–502.

22. Cepoiu-Martin M, Tam-Tham H, Patten S, Maxwell CJ, Hogan DB. Predictors of long-term care placement in persons with dementia: a systematic review and meta-analysis. Int J Geriatr Psychiatry 2016; 31: 1151–1171.

23. Huber M, Knottnerus JA, Green L, Van der Horst H, Jadad AR, Kromhout D, et al. How should we define health? BMJ 2011; 343: 1–3.

SUMMARY

Huntington's disease (HD) is a progressive neurodegenerative disorder caused by an autosomal dominantly inherited cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene on chromosome 4. The disease is clinically characterized by motor impairment, cognitive decline, and behavioral symptoms. As HD progresses, the symptoms lead to functional decline and loss of independency. The mean age of disease onset is 30-50 years and mean disease duration is 17-20 years. HD is presently incurable and it is not possible to delay either onset or progression of the disease.

In this thesis we have investigated measurement properties of the Unified Huntington's Disease Rating Scale (UHDRS) and the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP) in various severity stages of HD. These assessment scales have been developed to monitor the presence, severity, and progression of symptoms systematically over time. To measure change of symptoms accurately, reliable and valid scales are essential. The UHDRS consists of a motor, cognitive, behavioral, and functional domain. The UHDRS-FAP comprises a motor, cognitive, somatic, and behavioral section, and is especially designed for patients with advanced HD.

The clinical assessment of motor symptoms in HD is usually performed with the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). The UHDRS-TMS consists of 31 items assessing chorea, dystonia, eye movements, bradykinesia/rigidity, and gait/balance. All items are rated on a 0 to 4 point scale, with 0 indicating normal findings and 4 indicating severe abnormalities. A high interrater reliability is desirable for the monitoring of symptoms and, therefore, a teaching video and an annual online certification has been developed and implemented. We have investigated the interrater reliability of the UHDRS-TMS and of its subitems in 944 first-time participants, who took part in the online UHDRS-TMS certification (**chapter 2**). The UHDRS-TMS, tandem walking, pronate/supinate hands left, and retropulsion pull test showed good interrater reliability. Poor interrater reliability was found for dystonia of the trunk, dystonia of the left and right upper extremity, dystonia of the left and right lower extremity, tongue protrusion, and rigidity arms left. We concluded that the rating of these items is difficult to interpret, probably as a consequence of the subjective nature of the response options. Another important outcome of this study was that raters performed significantly worse on follow-up certification compared to their first certification. Therefore, we recommended that raters should watch the UHDRS-TMS teaching video before each certification.

For research purposes, the UHDRS-TMS is also used to distinguish between premanifest individuals (HD gene carriers who do not show symptoms yet) and manifest patients (HD gene carriers who have developed symptoms). We have examined if the oculomotor items of the UHDRS-TMS were affected in premanifest gene carriers compared to healthy controls (**chapter 3**), since oculomotor deficits have been detected by eye-tracking

equipment before HD onset. Seventy premanifest individuals and 27 controls were assessed. Horizontal ocular pursuit was the only oculomotor item that was more frequently affected in premanifest individuals near to HD onset compared to controls. Vertical ocular pursuit, horizontal and vertical saccade initiation, and horizontal and vertical saccade velocity did not show this. We hypothesized that only horizontal ocular pursuit is sensitive enough to detect early oculomotor deficits in individuals at risk for developing HD.

In patients with advanced HD, ceiling and floor effects of the UHDRS hamper the monitoring of HD changes. Therefore, the UHDRS-FAP has been developed voor late stage HD. We have studied the properties of the UHDRS-FAP and UHDRS in 40 patients with advanced HD residing in a nursing home or receiving day-care (**chapter 4**). Both assessment scales were administered on the same day and were repeated after seven days by an independent medical doctor. Severity of HD was divided into five stages using the Total Functional Capacity (TFC) subscale of the UHDRS; stage 1 included patients with early HD and stage 5 included patients with advanced HD. The motor scores of the UHDRS-FAP and UHDRS were the only subscales with significantly worse scores in TFC stage 5 compared to TFC stage 4. Further investigation suggested that the UHDRS-FAP motor score differentiated better between patients in the highest TFC stages than the UHDRS motor score (UHDRS-TMS). We concluded that the UHDRS-FAP motor score can possibly improve disease monitoring and, subsequently, care in patients with late stage HD in nursing homes. Additionally, a high internal consistency and high interrater reliability were found for the motor and cognitive scores of both assessment scales.

We have continued our study in advanced HD by administrating the UHDRS-FAP and UHDRS again after six months in 29 patients (**chapter 5**). The motor and cognitive scores of the UHDRS-FAP deteriorated during six months follow-up, while the motor and cognitive scores of the UHDRS did not show any change. This finding suggested that the UHDRS-FAP can detect disease progression in late stage HD, contrary to the UHDRS. Therefore, we recommended the use of the UHDRS-FAP motor and cognitive scores in long-term care facilities to optimize HD care by monitoring disease progression and by evaluating the effect of interventions in clinical care. The Functional Assessment Scale (FAS) and Independence Scale (IS) of the UHDRS functional domain, and the Care Dependency Scale (CDS) also declined over six months' time. Interestingly, the behavioral scores of the UHDRS-FAP and UHDRS improved in HD patients in TFC stages 4 and 5. We hypothesized that psychiatric symptoms fade away as the disease progresses due to emotional blunting and decreased insight.

In the same cohort of advanced HD patients, we have investigated the demographical and clinical differences between 28 nursing home residents and 12 patients receiving day-care

(**chapter 6**). Day-care participants were more often married than nursing home residents and were functionally more independent: the FAS was significantly higher. No correlations were found between institutionalization and motor disturbances, cognitive performance, and psychiatric symptoms. Not being married was the most predictive factor for nursing home admission. We concluded that a partner possibly assists with common daily tasks which a patient could not have done independently, resulting in being able to live at home longer. We hypothesized that providing support to unmarried patients by home care services specialized in HD may lead to interventions and treatment strategies that postpone the need for nursing home admission.

In conclusion, HD motor symptoms were reliable assessed with the UHDRS-TMS. However, future studies are required to explore how the dystonia items can be improved. In patients with advanced HD, the UHDRS-FAP was more sensitive to detect changes over time than the UHDRS and should, therefore, be implemented in nursing homes. Marriage was a protector for nursing home admission. However, future research should focus on the role of caregivers in postponing institutionalization.

NEDERLANDSE SAMENVATTING

De ziekte van Huntington (ZvH) is een progressieve neurodegeneratieve aandoening, die veroorzaakt wordt door een autosomale dominante overervende cytosine-adenine-guanine (CAG) trinucleotide verlenging in het Huntingtine gen op chromosoom 4. De ziekte wordt klinisch gekarakteriseerd door motorische verslechtering, cognitieve achteruitgang en gedragsproblemen. Als de ZvH vordert, leiden de symptomen tot functionele achteruitgang en verlies van onafhankelijkheid. De gemiddelde leeftijd waarop de ziekte zich manifesteert is tussen de 30 en 50 jaar en de gemiddelde duur van de ziekte is 17 tot 20 jaar. De ZvH is op dit moment een ongeneeslijke ziekte en het is niet mogelijk om het begin van de ziekte uit te stellen, dan wel progressie van de ziekte te remmen.

In dit proefschrift hebben we onderzoek gedaan naar de meeteigenschappen van de Unified Huntington's Disease Rating Scale (UHDRS) en de Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP) in verschillende stadia van de ZvH. Deze scorelijsten zijn ontwikkeld om de aanwezigheid, ernst en progressie van symptomen systematisch te volgen over de tijd. Om verandering van symptomen nauwkeurig te meten, zijn betrouwbare en valide scorelijsten essentieel. De UHDRS bestaat uit een motorisch, cognitief, functioneel en gedragsdomein. De UHDRS-FAP omvat een motorisch, cognitief, somatisch en gedragsdomein, en is speciaal ontwikkeld voor patiënten met vergevorderde ZvH.

De klinische beoordeling van motorische symptomen bij de ZvH wordt doorgaans verricht met behulp van de Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). De UHDRS-TMS bestaat uit 31 items, waarmee chorea, dystonie, oogbewegingen, bradykinesie/rigiditeit en lopen/balans worden beoordeeld. Alle items kunnen gescoord worden van 0 tot en met 4, waarbij 0 'normale bevindingen' en 4 'ernstige afwijkingen' aangeeft. Om symptomen te meten is een hoge interbeoordelaarsbetrouwbaarheid wenselijk. Daarom is een onderwijsvideo en een jaarlijkse online certificatie ontwikkeld en ingevoerd. Wij hebben de interbeoordelaarsbetrouwbaarheid van de UHDRS-TMS en van de subitems onderzocht in 944 deelnemers die voor het eerst meededen aan de online UHDRS-TMS certificatie (**hoofdstuk 2**). De UHDRS-TMS, koorddansersgang, pronatie/supinatie linkerhand en de retropulsietest hadden een goede interbeoordelaarsbetrouwbaarheid. Een slechte interbeoordelaarsbetrouwbaarheid werd gevonden voor dystonie van de romp, dystonie van de linker- en rechterarm, dystonie van het linker- en rechterbeen, tongprotrusie en rigiditeit van de linkerarm. Wij concludeerden hieruit dat de scoring van deze items moeilijk te interpreteren is, waarschijnlijk als gevolg van de subjectiviteit van de antwoordmogelijkheden. Een andere belangrijke bevinding van dit onderzoek was dat de deelnemers significant slechter scoorden tijdens hun tweede certificatie vergeleken met hun eerste certificatie. We hebben daarom geadviseerd dat deelnemers de UHDRS-TMS onderwijsvideo voor elke certificatie opnieuw moeten kijken.

In onderzoeksverband wordt de UHDRS-TMS ook gebruikt om onderscheid te maken tussen premanifeste personen (gendragers die nog geen symptomen hebben) en manifeste patiënten (gendragers die wel symptomen hebben ontwikkeld). We hebben onderzocht of de oogbewegingsitems van de UHDRS-TMS waren aangedaan in premanifeste gendragers vergeleken met gezonde controles (**hoofdstuk 3**), aangezien met gecomputeriseerde apparatuur afwijkingen van de oogbewegingen waren gevonden vóór het begin van de ZvH. Zeventig premanifeste personen en 27 controles werden onderzocht. Horizontale oogvolgbewegingen waren het enige oogbewegingsitem dat frequenter was aangedaan in premanifeste personen dichtbij begin van de ziekte vergeleken met controles. Voor de verticale oogvolgbewegingen, horizontaal en verticaal begin van de saccade en horizontale en verticale snelheid van de saccade gold dit niet. Wij veronderstelden dat horizontale oogvolgbewegingen als enige sensitief genoeg waren om beginnende afwijkingen van de oogbewegingen te detecteren bij risicodragers.

Bij patiënten met vergevorderde ZvH belemmeren plafond- en bodemeffecten van de UHDRS het vastleggen van veranderingen. Voor patiënten in een laat stadium van de ZvH is daarom de UHDRS-FAP ontwikkeld. Wij hebben de eigenschappen van de UHDRS-FAP en de UHDRS onderzocht bij 40 patiënten met vergevorderde ZvH, die in een verpleeghuis woonden of daar dagbehandeling kregen (**hoofdstuk 4**). Beide scorelijsten werden afgenomen op dezelfde dag en werden na zeven dagen herhaald door een onafhankelijke arts. De ernst van de ZvH werd verdeeld in vijf stadia door middel van de Total Functional Capacity (TFC) schaal van de UHDRS; stadium 1 bestond uit patiënten met een vroeg stadium van de ZvH en stadium 5 bestond uit patiënten met een laat stadium van de ZvH. De motorische scores van de UHDRS-FAP en UHDRS waren de enige domeinen met een significant slechtere score in TFC stadium 5 vergeleken met TFC stadium 4. Verder onderzoek deed vermoeden dat de motorische score van de UHDRS-FAP beter differentieerde tussen patiënten in de hoogste TFC stadia dan de motorische score van de UHDRS (UHDRS-TMS). We hebben hieruit geconcludeerd dat de motorische score van de UHDRS-FAP mogelijk het monitoren van de ziekte kan verbeteren, en dientengevolge ook de zorg, bij patiënten in een laat stadium van de ZvH in verpleeghuizen. Daarnaast werden ook een hoge interne consistentie en hoge interbeoordelaarsbetrouwbaarheid gevonden voor de motorische en cognitieve scores van beide scorelijsten.

We hebben onze studie in 29 patiënten met vergevorderde ZvH voortgezet door de UHDRS-FAP en UHDRS nogmaals af te nemen na zes maanden (**hoofdstuk 5**). De motorische en cognitieve scores van de UHDRS-FAP verslechterden na zes maanden, terwijl de motorische en cognitieve scores van de UHDRS niet veranderden. Deze uitkomst impliceert dat de UHDRS-FAP, in tegenstelling tot de UHDRS, ziekteprogressie kan detecteren bij patiënten in een laat stadium van de ZvH. We hebben daarom geadviseerd om de motorische en cognitieve scores van de UHDRS-FAP te gebruiken in verpleeghuizen

om de zorg te verbeteren door middel van het meten van ziekteprogressie en het evalueren van het effect van interventies. De Functional Assessment Scale (FAS) en de Independence Scale (IS) van het functionele domein van de UHDRS en de Care Dependency Scale (CDS) verslechterden ook na zes maanden. De gedragsscores van de UHDRS-FAP en de UHDRS verbeterden juist bij patiënten met de ZvH in TFC stadia 4 en 5. Wij vermoedden dat psychiatrische symptomen afnemen door emotionele vervlakking en afgenomen ziekte-inzicht als de ziekte vordert.

In hetzelfde cohort van patiënten met vergevorderde ZvH hebben we de demografische en klinische verschillen onderzocht tussen 28 verpleeghuisbewoners en 12 patiënten die dagbehandeling kregen (**hoofdstuk 6**). De deelnemers met dagbehandeling waren vaker getrouwd dan de verpleeghuisbewoners en waren zelfstandiger: de FAS was significant hoger. Er werden geen correlaties gevonden tussen verpleeghuisopname en motorische verschijnselen, cognitieve prestaties en psychiatrische symptomen. Niet getrouwd zijn had de grootste voorspellende waarde voor verpleeghuisopname. We concludeerden hieruit dat een partner waarschijnlijk helpt bij dagelijkse taken die een patiënt niet zelfstandig had kunnen doen, wat ervoor zorgt dat iemand langer thuis kan blijven wonen. We veronderstelden daarom dat hulp aan ongetrouwde patiënten door thuiszorginstanties die gespecialiseerd zijn in de ZvH zou kunnen leiden tot interventies en behandelingsstrategieën die verpleeghuisopname kunnen uitstellen.

Concluderend, zijn de motorische symptomen van de ZvH betrouwbaar vast te stellen met de UHDRS-TMS. Er zijn echter wel studies nodig om te onderzoeken hoe, met name, de dystonie items verbeterd kunnen worden. Bij patiënten met vergevorderde ZvH was de UHDRS-FAP sensitiever dan de UHDRS wat betreft het detecteren van veranderingen gedurende de tijd en daarom zou de UHDRS-FAP geïmplementeerd moeten worden in verpleeghuizen. Het huwelijk bleek een beschermer voor verpleeghuisopname. Verder onderzoek is echter nodig om de rol van partners/verzorgers in het uitstellen van verpleeghuisopname in kaart te brengen.

List of publications

Winder JY, Roos RAC. Premanifest Huntington's disease: examination of oculomotor abnormalities in clinical practice. PLos ONE 2018; 13: 1–8.

Winder JY, Roos RAC, Burgunder J-M, Marinus J, Reilmann R. Interrater reliability of the Unified Huntington's Disease Rating Scale-Total Motor Score certification. Mov Disord Clin Pract 2018; 5: 290–295.

Winder JY, Achterberg WP, Marinus J, Gardiner SL, Roos RAC. Assessment scales for patients with advanced Huntington's disease: comparison of the UHDRS and UHDRS-FAP. Mov Disord Clin Pract 2018; 5: 527–533.

Winder JY, Achterberg WP, Roos RAC. Marriage as protector for nursing home admission in Huntington's disease. J Huntingtons Dis 2018; 7: 251–257.

Winder JY, Achterberg WP, Gardiner SL, Roos RAC. Longitudinal assessment of the Unified Huntington's Disease Rating Scale (UHDRS) and UHDRS-For Advanced Patients (UHDRS-FAP) in patients with late stage Huntington's disease. Eur J Neurol 2019; 0: 00–00.

Van Diemen MPJ, Hart EP, Kan H, Van der Grond J, Bergheanu S, Abbruscato A, Mead L, Coppen EM, **Winder JY**, Van Beelen I, Webb A, Roos RAC, Groeneveld G-J. A two-part study to assess the safety, pharmacokinetics and pharmacodynamics of SBT-020 in patients with early stage Huntington's disease. *Submitted*.

Van Diemen MPJ, Van Beelen I, Hart EP, Hameeteman PW, Coppen EM, **Winder JY**, Den Heijer J, Moerland M, Kan H, Van der Grond J, Webb A, Roos RAC, Groeneveld G-J. Brain bio-energetic state is not correlated to muscle mitochondrial capacity in Huntington's disease. *Submitted*.

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Curriculum vitae

Jessica Winder werd geboren op 14 januari 1989 in Alkmaar. Na het behalen van haar gymnasiumdiploma aan het Murmellius Gymnasium in Alkmaar in 2007, begon zij aan de studie geneeskunde aan de Vrije Universiteit in Amsterdam. Een deel van haar coschappen deed ze in het Steve Biko Academic Hospital in Pretoria, Zuid-Afrika. Tijdens haar coschappen werd ze geboeid door de neurologie en koos ze ervoor haar semi-artsstage te doen op de afdeling neurologie in het toenmalige Kennemer Gasthuis in Haarlem (nu Spaarne Gasthuis). In 2013 studeerde ze af als arts en werkte achtereenvolgens als ANIOS neurologie in het Groene Hart Ziekenhuis in Gouda en het toenmalige Medisch Centrum Haaglanden in Den Haag (nu Haaglanden Medisch Centrum), waar ze de basis legde voor haar klinische vaardigheden. Door haar belangstelling voor bewegingsstoornissen, begon ze in 2015 aan een promotietraject naar de ziekte van Huntington in het Leids Universitair Medisch Centrum in Leiden onder begeleiding van prof. dr. R.A.C. Roos en prof. dr. W.P. Achterberg. Haar promotieonderzoek richtte zich specifiek op de UHDRS en UHDRS-FAP scorelijsten die bij de ziekte van Huntington gebruikt worden. Zij heeft een deel van de klinische gegevens voor haar onderzoek verzameld in het Huntington Centrum Topaz Overduin in Katwijk. Tevens heeft ze tijdens haar promotietraject als uitvoerend onderzoeker gewerkt voor de internationale studies Enroll-HD, LEGATO-HD en Trihep3-HD. Na haar promotieonderzoek heeft ze kortdurend als ANIOS neurologie in het OLVG in Amsterdam gewerkt en nu is zij werkzaam als ANIOS neurologie in het Erasmus MC in Rotterdam.