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

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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.

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