Unified Huntington’s Disease Rating Scale: clinical practice and a critical approach

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Summary
The purpose of this study was to test the usefulness of the Unified Huntington’s Disease Rating Scale (UHDRS) in clinical practice.

The UHDRS was used to examine 45 persons with genetically diagnosed Huntington’s disease (HD) in various stages.

The rate of motor involvement, cognitive deficit and reliance on nursing care rose in linear proportion to HD duration. The severity of motor involvement correlated significantly with all UHDRS subscales except for that of behavioral disorders, the rate of these disorders being unrelated to any of the parameters under study. The number of CAG triplets was inversely correlated with the age at onset of HD.

Being considerably time consuming, administration of the whole UHDRS calls for interdisciplinary co-operation. For valid data acquisition, the participation of caregivers is also essential. In clinical practice it is advisable regularly to monitor the patient’s conditions and the efficacy of treatment using the UHDRS motor, functional and behavioral subscales. Cognitive tests present difficulties but, in view of the progressive cognitive deterioration in HD, they are very useful in the early stage of the disease. The UHDRS does not assess impaired voluntary motor activity, or furnish information relating to therapy, dysphagia, weight loss, sexual problems or drug abuse.

KEY WORDS: behavioral disorders, CAG triplets, cognitive deficit, executive dysfunction, Huntington’s disease, Unified Huntington’s disease rating scale.

Introduction
Huntington’s disease (HD) is an autosomal dominant inherited neurodegenerative disease. The main symptoms of HD are choreatic movements with impaired voluntary motor activity, behavioral disorders, and progressive cognitive deterioration leading to dementia.

A number of scales and batteries of tests designed to evaluate the HD patient’s motor and cognitive deficits, behavioral disturbances, and daily activities are in use worldwide (1-4).

In 1996, an international Huntington’s Disease Study Group (5) came forward with their Unified Huntington’s Disease Rating Scale (UHDRS). This is a collection of scales, tests and questionnaires allowing comprehensive clinical rating of HD severity. The UHDRS assesses the severity of motor impairment (UHDRS-motor assessment, UHDRS-M), as well as the degree of cognitive deterioration (cognitive assessment, UHDRS-psychology UHDRS-P). Disorders of behavior and of mentation are investigated by means of the UHDRS-behavioral assessment (UHDRS-B). Questionnaires such as UHDRS-functional assessment (UHDRS-F), UHDRS-independence (UHDRS-I) and UHDRS-functional capacity (UHDRS-C) are designed to evaluate HD patients’ self-care, and social and financial needs.

The purpose of the present study was to evaluate the usefulness of the UHDRS in clinical practice and to clarify the relationship between motor, cognitive and behavioral findings and CAG triplet repeats.

Materials and methods
We studied 45 patients (17 men, 28 women) with genetically confirmed HD in various stages.

The following parameters were assessed: actual age, age at clinical onset and duration of HD (retrospectively established), and pathological number of CAG triplet repeats (Table I, over).

The patients were tested in accordance with the UHDRS protocol (5). A neurologist assessed the severity of the motor symptomatology, as well as the patients’ behavior, independence and functional capacity.

The neuropsychological examination, on the other hand, was performed by a clinical psychologist using the Czech version of cognitive tests, in particular: the Digit Symbol Modalities Test (DSMT) (6), the Verbal Fluency Test (VF) (7), and the Stroop Test. In particular, the shortened (45-second) Stroop Test used in the UHDRS was replaced by a Czech version of a previous, unpublished adaptation of the Stroop Test (Regard M. Cognitive rigidity and flexibility: a neuropsychological study. Ph.D. dissertation, University of Victoria, British Columbia, 1981).
In addition, the Mini Mental State Examination (MMSE) was used to test the patients’ global cognitive deficit (8) (Table I).

**Statistical analysis**

The data thus obtained were statistically analyzed using the SPSS 11.5 programme (Chicago, Illinois). The results of the Spearman’s correlation analysis were post-hoc corrected using the Bonferroni correction for multiple comparisons.

**Results**

Detailed information on the present age, age at clinical onset and duration of HD, CAG triplet repeats, and UHDRS and MMSE deficits is given in Table I. The correlations between the parameters in our cohort were analyzed by means of the non-parametric Spearman correlation test. The results of this analysis are listed in Table II. For easier review, the results of the correlation analysis in our cohort can be summed up as follows.

An inverse correlation between the number of CAG triplet repeats and the age at clinical onset of HD was confirmed. The number of triplet repeats had no influence on the degree of motor or cognitive affection or behavioral disturbances. HD duration was directly proportional to the progressively worsening motor and cognitive deficits and to the need for nursing care. Significant correlations were found between all the UHDRS sub-scales, except for UHDRS-B. Global cognitive deficit, as determined by the MMSE, correlated well with HD duration but also with the severity of the motor disorders and with the UHDRS-measured cognitive deficit. In our cohort, no interdependence was found between behavioral changes and motor, functional or cognitive deficiency.

**Discussion**

**Motor impairment**

As expected, the degree of motor involvement expressed in terms of UHDRS-M rose with increasing HD duration. Typically, HD is noted for a slow build-up of motor impairment ultimately leading to major disability. Increasing overall motor impairment does not, however, reflect a proportionally increasing severity of all the symptoms quantified in the UHDRS-M. Some manifestations, such as chorea, will often show an abatement while in the intermediate and late stages HD is compounded by dystonia and akinesia with rigidity. Other symptoms, such as oculomotor disorders, continue to

<table>
<thead>
<tr>
<th>Table I - Descriptive statistical analysis of the cohort.</th>
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<tbody>
<tr>
<td><strong>Arith. mean</strong></td>
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<tr>
<td>Present age (yrs)</td>
</tr>
<tr>
<td>Age at HD onset (yrs)</td>
</tr>
<tr>
<td>HD duration (yrs)</td>
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<tr>
<td>CAG triplets (no.)</td>
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</tbody>
</table>

Rating scale scores

- **UHDRS-M**: 17.27, **SD**: 8.64, **Max.**: 38.00, **Min.**: 3.00, **Range**: 35.00
- **VF**: 15.49, **SD**: 8.55, **Max.**: 39.00, **Min.**: 3.00, **Range**: 36.00
- **DSMT**: 19.45, **SD**: 10.24, **Max.**: 55.00, **Min.**: 0.00, **Range**: 55.00
- **Stroop - part 1**: 32.75, **SD**: 17.86, **Max.**: 94.00, **Min.**: 13.00, **Range**: 81.00
- **Stroop - part 2**: 44.45, **SD**: 27.61, **Max.**: 146.00, **Min.**: 19.00, **Range**: 127.00
- **Stroop - part 3**: 84.59, **SD**: 52.16, **Max.**: 236.00, **Min.**: 31.00, **Range**: 205.00
- **UHDRS-B**: 11.49, **SD**: 7.38, **Max.**: 27.00, **Min.**: 0.00, **Range**: 27.00
- **UHDRS-depression**: 8.64, **SD**: 5.81, **Max.**: 18.00, **Min.**: 0.00, **Range**: 18.00
- **UHDRS-irritability**: 4.04, **SD**: 3.73, **Max.**: 11.00, **Min.**: 0.00, **Range**: 11.00
- **UHDRS-OCD**: 3.02, **SD**: 2.71, **Max.**: 8.00, **Min.**: 0.00, **Range**: 8.00
- **UHDRS-psychosis**: 0.00, **SD**: 0.00, **Max.**: 0.00, **Min.**: 0.00, **Range**: 0.00
- **UHDRS-F**: 16.60, **SD**: 5.02, **Max.**: 24.00, **Min.**: 4.00, **Range**: 20.00
- **UHDRS-I**: 77.78, **SD**: 15.80, **Max.**: 100.00, **Min.**: 50.00, **Range**: 50.00
- **UHDRS-C**: 6.82, **SD**: 3.63, **Max.**: 12.00, **Min.**: 2.00, **Range**: 10.00
- **MMSE**: 23.02, **SD**: 3.63, **Max.**: 29.00, **Min.**: 15.00, **Range**: 14.00

Abbreviations: HD=Huntington’s disease; UHDRS-M=Unified Huntington’s Disease Rating Scale-motor deficit; VF=Verbal Fluency Test; DSMT=Digit Symbol Modalities Test; UHDRS-B=overall behavioral score; UHDRS-depression=symptoms of depression; UHDRS-irritability=irritability, aggressive behavior; UHDRS-OCD=obsessive-compulsive behavior; UHDRS-F=functional assessment; UHDRS-I=independence; UHDRS-C= functional capacity; MMSE=Mini Mental State Examination.
worsen over time. The increasing score in the late stages of the disease is due mainly to the progression of gait and postural stability disorders. The UHDRS-M covers all the main motor signs in HD, with the exception of the disordered voluntary movements. In fact, the latter, in the context of the multitude of involuntary movements and of the akinesia, for example, would be very difficult to test and to interpret. Furthermore, some of the proposed assessment modalities, e.g., fist-hand-palm test, are strongly dependent on executive functions.

Cognitive impairment

Our patients' cognitive performances were significantly impaired in all the tests. The VF, DSMT and Stroop tests are among the basic tests of executive functions. These functions are closely dependent, anatomically and functionally, on the frontal cortex. As for the cognitive tests administered in our cohort, deficient performance on the DSMT was found to correlate best with HD duration. The DSMT is one of the most sensitive tests for monitoring HD progression (9). Decreased performance on the DSMT has also been noted in persons at risk of HD several years before the appearance of any clinical manifestation (10,11). The DSMT is designed to test not only executive dysfunction but also psychomotor speed, short-term memory and visuomotor skills.

Going by our results, the VF, too, is good for detecting HD onset and, in particular, for monitoring the progression of cognitive deterioration. All our patients exhibited a significantly impaired VF. There was a striking deficit in VF even in patients with incipient HD who were otherwise performing normally on the MMSE. Performance on the VF was seen to worsen steadily (reflecting executive dysfunction) with increasing HD duration. Of the many different versions of the Stroop test, the shorter version is recommended in the initial stages of the disease, on the grounds of its sensitivity and the HD patients' marked cognitive deficits and dysarthria. To save time, and also in view of the patients' cognitive limitations, the longer versions of the tests, which HD patients find tiring and demotivating, can be avoided. In our experience, the short Victoria version of the Stroop test (Regard M, unpublished data) provides sufficient and sensitive assessment of selective attention capacity. The results obtained using this version showed an obvious deficit in all of the patients.

The MMSE investigates the presence of global cognitive deficiency. The overall MMSE score in our cohort correlated very well (as did tests of executive functions in the UHDRS) with the motor and functional deficits as assessed using the UHDRS-M and UHDRS-F. Going by our own experience, patients in the initial stages of HD often attain normal performance levels in the MMSE. While initially coping with MMSE, HD patients first fail in tasks dependent on executive functions (free recall, serial 7s test) and in the visual-construction task (copies of geometric figures). We found the MMSE rather useful for the monitoring of HD progression in subjects with medium to severe cognitive deficit. Frequent and re-

Table II - Spearman's correlation analysis.

<table>
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<tr>
<th></th>
<th>Present age</th>
<th>Age at HD onset</th>
<th>HD duration</th>
<th>CAG triplet repeats</th>
<th>UHDRS-M</th>
<th>VF</th>
<th>DSMT</th>
<th>Stroop part 1</th>
<th>Stroop part 2</th>
<th>Stroop part 3</th>
<th>UHDRS-B</th>
<th>UHDRS-depression</th>
<th>UHDRS-irritability</th>
<th>UHDRS-OCD</th>
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<td>.232</td>
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<td>.761**</td>
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<td>.047</td>
<td>-.001</td>
<td>-.062</td>
<td>.489**</td>
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<td>-.136</td>
<td>.233</td>
<td>.192</td>
<td>.197</td>
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<td>-.401**</td>
<td>-.128</td>
<td>-.653**</td>
<td>-.566**</td>
<td>-.639**</td>
<td>-.650**</td>
<td>-.624**</td>
<td>-.600**</td>
<td>-.043</td>
<td>-.086</td>
<td>-.007</td>
<td>.331*</td>
</tr>
</tbody>
</table>

Abbreviations and symbols: HD=Huntington's disease; UHDRS-M=Unified Huntington's Disease Rating Scale-motor deficit; VF=Verbal Fluency Test; DSMT=Digit Symbol Modalities Test; UHDRS-B=overall behavioral score; UHDRS-depression=symptoms of depression; UHDRS-irritability=irritability, aggressive behavior; UHDRS-OCD=obsessive-compulsive behavior; MMSE=Mini Mental State Examination.

** Statistically significant correlation p<0.01; * Statistically significant correlation p<0.05; Relevant significance after Bonferroni correction is indicated in bold **p<0.01.
peated detailed neuropsychological testing of patients with straightforward dementia is redundant, barely within their capabilities, or downright unfeasible. Patients find such testing exhausting or frustrating, and this is without mentioning the conceivable effects of retesting. In contrast to the cognitive tests within the UHDRS, the MMSE offers the advantage of being easy to use, even by physicians with little experience in the field of neuropsychology.

Relationship between motor and cognitive impairment

In our study, as in others, there emerged a significant correlation between motor and cognitive performance (5,12,13). Impaired movement initiation and execution is bound to limit markedly the speed of written responses (DSMT, MMSE) and spoken (VF, Stroop, MMSE) utterances. This statistical dependence can also be explained by the fact that HD involves degeneration of the striatum and other regions of the brain (14) that participate simultaneously in the control of motor and cognitive activities. The rate of occurrence of each of the motor and mental symptoms appears to depend on the degree of involvement of specific areas of the striatum and their connections. The particular deficits can thus develop at different rates, in parallel with, or partially or entirely independently of each other, just as they can potentiate each other. Proof of these assertions can be found not only in lesion-related studies (15,16) but also in the different clinical course of the late (17) and juvenile (18) forms of HD.

Behavioral disorders

The UHDRS-B covers the salient behavioral symptoms seen in HD. However, there is no scoring of apathy, often one of the prominent symptoms of HD, already present at the onset of the disease (4). Similarly, there is no option for assessing cases of mania, which, on the other hand, is a relatively rare feature of HD (19).

Nor does the UHDRS-B take into account the patient’s own perception of his/her state of health, sexual problems, alcohol abuse, smoking or drug addiction; instead, it is concerned only with the patient’s present conditions (ignoring important anamnestic data - occurrence of depression, suicidal behavior, aggression, psychotic symptoms, criminal activities).

However, testing HD patients for behavioral disorders is considerably time consuming and very demanding for a less experienced physician. Ideally, the interview should be conducted by a psychiatrist or a psychologist. Cooperation on the part of the patient’s caregivers is also likely to increase the validity of the examination. In view of all these considerations, in this study, we used only the overall raw UHDRS-B score for statistical analysis. Symptoms of depression and anxiety in our cohort predominated over those of irritability and aggression. While no psychotic symptoms were detected in the course of the examinations, this does not, in our view, mean that they were absent. It may be that they could not be detected using a neurologist-conducted structured interview.

Like motor and cognitive symptoms, behavioral disorders are, at least in part, dependent on the same brain structures (16). This again points to a possible selectivity in the involvement of different cerebral regions or specific neuronal subpopulations (14).

In our study we did not find any relationship between behavioral disorders and other parts of the UHDRS. One of the explanations as to why behavioral disturbances are uncorrelated with the motor and cognitive impairment seen in HD may lie in the variability and overlapping of different behavioral symptoms which are, consequently, very difficult to scale-rate and interpret. Under-estimation of the behavioral symptoms in HD patients could be, in our opinion, due to the developing signs of apathy, which the UHDRS-B does not take into account. Similarly, as in our report, most authors study patients already being treated with antipsychotics, antidepressives and benzodiazepines, which can abate or mask a number of behavioral symptoms.

Functional impairment

In our cohort, the disease duration and growing cognitive affection correlated with the patients’ increasing dependence on other people’s assistance. All our patients had to give up their jobs, and found themselves unable to cope even with less demanding work. They had problems with activities of daily living (ADL) from the very onset of HD. Even those patients with sufficient cognitive capacity were restricted by their motor incoordination. The data contained in the UHDRS-C assessment (disability expressed in per cent) and UHDRS-I (self-care, management of finances, work, assistance-dependence, etc.) amount to nothing more than another interpretation of the more detailed information contained in the UHDRS-F. This is why, in our view, the UHDRS-C and the UHDRS-I fail to yield meaningful new data on these patients or their needs.

As in the case of behavioral disorders, functional deficits should be assessed together with the patient’s family or caregivers, an aspect not included in the UHDRS methodology.

What the whole UHDRS fails to collect are particulars of food intake and state of nutrition. In HD, it is typical for patients gradually to lose weight as the disease progresses (20). Hence, they should be weighed at every follow-up visit, and asked about their appetite and about possible signs of dysphagia.

CAG triplet repeats and clinical course

Our study confirmed the known fact that the number of CAG triplet repeats correlates inversely with the age at onset of HD (21). Like other authors, we failed to find any connection between the CAG triplet repeats and the severity of motor (22) or cognitive (23) involvement. Nor could we prove any correlation between the overall score of behavioral disorders (UHDRS-B) and the CAG triplet repeats. This again tallies with the outcome of previous studies (5,12,13). Craufurd et al. (4) was able to note rather more expressed symptoms of apathy in patients with larger numbers of CAG triplets. In our opinion, assessing data on the number of CAG triplets without taking into consideration the patient’s age at onset of HD and the duration of the disease makes little sense, because the
number of CAG triplets is a stationary parameter, whereas motor and cognitive impairments are progressive. That said, our cohort was not sufficiently large for this mode of assessment.

Conclusion

Our experience with the UHDRS so far is limited by the rather small number of patients under study, but we believe we can already judge the scale as beneficial for our clinical practice within the Movement Disorders Center. We believe that the UHDRS-M subscale is a practical and rapid instrument for assessing and following up the development of motor involvement.

The UHDRS-B is a useful guide for structured interviews targeted at HD psychopathology, but it does not cover all the behavioral symptoms. Appropriate and detailed testing of behavioral disturbances is time-consuming and ought to be done by psychiatrists or clinical psychologists. We have often seen evidence of our own lack of expertise in behavioral disorders. With the exception of the UHDRS-B, all the parts of the UHDRS are intercorrelated.

A lack of internal consistency between UHDRS-B and other parts of the UHDRS may indicate clinical underestimation or independence of behavioral disorders. Again, measuring the extent and depth of cognitive deterioration requires neuropsychological expertise.

The UHDRS-F, too, provides a relatively good estimate of the degree of ADL limitation. In contrast, the UHDRS-C and UHDRS-I fail to yield relevant new information about the patient, and, in our opinion, one can speculate on the usefulness of these scales.

The whole UHDRS helps in the detection and follow up of HD progression, but also in the assessment of the degree of ADL limitation. In contrast, the UHDRS-C and UHDRS-I fail to yield relevant new information about the patient, and, in our opinion, one can speculate on the usefulness of these scales.

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References