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Rating Scales for Motor Symptoms and Signs in Huntington's Disease: Critique and Recommendations

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Abstract: Motor symptoms are a major feature of Huntington's disease (HD). The International Parkinson and Movement Disorder Society (MDS) commissioned the assessment of the clinimetric properties of motor rating scales in HD to make recommendations regarding their use, following previously established standardized criteria. After a systematic literature search, a total of 6 rating scales assessing motor symptoms and signs in HD were included for review. Performance testing (reviewed elsewhere) and quantitative motor rating methods were excluded. Only the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) was classified as "recommended" for assessing the severity of motor signs in HD. The following scales were classified as "suggested": Abnormal Involuntary Movement Scale, the UHDRS-TMS4, the Quantified Neurological Examination, and the Marsden and Quinn Chorea Severity Scale. The committee also concluded that further assessment of existing rating scales, including the UHDRS-TMS, is necessary to determine sensitivity to change and to screening for the presence of motor signs specific to HD. There is also a need to develop a motor rating scale to be used in positive gene carriers with subtle but not definite motor signs.

Motor abnormalities are a core feature of Huntington's disease (HD) to such an extent that HD is also known as Huntington's chorea. Motor symptoms and signs continue to be used as the main reference for a clinical diagnosis of HD in both clinical practice and research.[1,2] Several rating scales are available to assess motor symptoms and signs in HD. Some of these rating scales were developed specifically for HD and are used to screen for the presence of motor features in HD, assess severity, or capture change in severity over time or after a therapeutic intervention in the setting of a clinical trial. However, the clinimetric properties of these measurement tools have not been fully described and compared. In this review, we assessed all motor clinical rating scales used in HD studies and critically appraised their context of use and status of clinimetric development in HD. Our ultimate goal is to provide recommendations for their future use, following the criteria defined by the International Parkinson and Movement Disorder Society (MDS). We defined the scope of this review by including rating scales

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that assess motor features per se, in contrast to measurement tools that assess the performance of motor tasks with significance for activities of daily living. These measures are the subject of another review that forms part of the MDS-sponsored project of reviewing all clinical rating scales used in HD, including clinical measurement tools that measure other clinical features of HD, such as cognitive impairment and behavioral problems.

Materials and Methods

We followed the methodology proposed by the MDS Committee on Rating Scales Development described elsewhere,[3] which includes (1) organization and critique process, (2) selection of scales, (3) inclusion/exclusion for review, and (4) criteria for rating scales. For the selection of scales, the keywords selected for this review were: "motor," "chorea," "dystonia," "parkinsonism," "balance," and "gait." For inclusion/exclusion of studies for the current review, we excluded any method of motor quantification that was developed or applied in HD, because this review was restricted to clinical rating scales (Tables 1).

Results

Identified Scales and their Use in Clinical Research

In total, 27 rating scales that have been used in HD, including different versions, were identified. After screening for exclusion criteria with abstract screening and in-depth review, a total of 6 motor rating scales were included (for more details, see online supporting information).

TABLE 1 *Classification System for Scale Recommendation*

Category	Criteria
"Recommended"	(1) Scale has been used in HD populations (2) Use in HD by groups other than the original developers and data on its use were available* (3) The available clinimetric/psychometric data in HD support the goals of screening (e.g., evaluation of sensitivity/specificity, score cutoff points, and reliability) or measurement of severity (e.g., evaluation of reliability, construct validity, and score discrimination across levels of symptom severity)
"Suggested"	(1) Scale has been used in HD populations (2) Only 1 other criteria (2) or (3) from the above-recommended category applies
"Listed"	(1) Scale has been used in HD populations, but no further criterion met

Abbreviation: HD, Huntington's disease.
*For rating scales not originally developed for use in HD, Criterion 2 was fulfilled if used in at least 1 group with HD that reported any kind of clinimetric/psychometric data on HD.

Critique of Clinical Motor Rating Scales

We provide a brief description of the clinical motor rating scales classified as "recommended" or "suggested" (Table 2) (for a full description of all included motor rating scales, including the Rockland-Simpson Dyskinesia Rating Scale and the Kartzinel, Hunt, Calne Scale, see online supporting information).

The Unified Huntington's Disease Rating Scale Motor Section *alias* Unified Huntington's Disease Rating Scale-Total Motor Score

The Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) is a clinician-rated scale that was developed by the Huntington Study Group to prospectively assess clinical features of HD in both patients with HD and individuals at risk for HD.[4] The entire UHDRS is composed of 6 sections (Motor, Cognitive, Behavioral, Functional Assessment, Independence Scale, and Total Functional Capacity). The UHDRS-TMS is formed of 15 items and has a maximum score of 124. The different items of the UHDRS-TMS include chorea, dystonia, parkinsonism, motor performance, oculomotor function, and balance. The original version was published in 1996[4] and was updated and expanded in 1999 (UHDRS 1999) with the intention to increase its applicability.[5] The dysarthria item was removed from the first version of the UHDRS-TMS, and the remaining composition of items was unchanged.[5] The UHDRS-TMS has been used in multiple observational studies and clinical trials beyond the group that developed it. It has been used in both premanifest and manifest HD populations. The scale is quick to use (approximately 5 minutes). Different item combinations of the UHDRS-TMS have been used: 4 shortened versions were published 1 year later (TMS1–4);[6] including a modified motor score[7] as well as reported sub-item scores focused on gait,[8] chorea,[9] and dystonia[10] or items related to bradykinesia.[11,12] Because clinimetric data are only available for the UHDRS-TMS and the reduced UHRDS-TMS1–4 (see below), only these were considered for detailed review.

Most clinimetric data from the UHDRS-TMS originate from the work performed by the scale's original developers in patients with manifest HD.[4] Internal consistency of the UHDRS-TMS has been reported as very good in manifest HD, with a Cronbach' α value ranging from 0.95 to 0.97.[4,6] For the UHDRS-TMS, 5 factors account for 79% of the total variance in the correlation matrix: a first factor (ocular pursuit, saccadic initiation and velocity, dysarthria, tongue protrusion, Luria, finger taps, gait, overall bradykinesia, pronate-supinate hand, rigidity, and tandem walk) accounts for 48% of the variance.[6] Very good test-retest reliability (0.96 and 0.97) has been reported in patients with manifest HD, although correlation coefficients were used.[6] Inter-rater reliability has been shown to be very good, with an intraclass correlation coefficient of 0.94, albeit in a small sample of patients with manifest HD (n = 24). In the same study, the interclass correlation

TABLE 2 *Summary of Suggested and Recommended Scales*

Scale/questionnaire	Developed for use in HD	Scale has been applied to HD populations	Used by other groups beyond the original developing group	Appropriate clinimetric testing in HD	Recommendation level
Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS)	Yes	Yes	Yes	Yes	"Recommended" for assessment of severity of motor signs in HD
UHDRS-TMS4	Yes	Yes	Yes	No	"Suggested" for assessment of severity of motor signs in HD
Quantified Neurological Examination	Yes	Yes	Yes	No	"Suggested" for assessment of severity of motor signs in HD
Marsden and Quinn Chorea Severity Scale	Yes	Yes	Yes	No	"Suggested" for assessment of severity of chorea in HD
Abnormal Involuntary Movement Scale	No	Yes	Yes	No	"Suggested" for assessing severity of chorea/dystonia in HD

Abbreviation: HD, Huntington's disease.

coefficient was lower for the chorea (0.82) and dystonia (0.62) subscores.[4] As expected, the UHDRS-TMS is negatively correlated with the UHDRS-Total Functional Capacity scale, as well as with other UHDRS functional scales,[4,6,13–15] and with cognitive scales.[4] Extensive data from multiple observational studies and clinical trials suggest that the UHDRS-TMS is sensitive to change over time,[11,16–21] but there has been no formal clinimetric assessment.

Recommendation

The UHDRS-TMS is "recommended" for the assessment of severity of motor signs in HD. The UHDRS-TMS is a widely used scale and is considered valid in manifest HD. The available clinimetric data document sufficient reliability and validity for the purposes outlined above in manifest HD, although responsiveness has not been formally tested.

Reduced Versions of the UHDRS-TMS

The different reduced versions of the UHDRS-TMS (TMS1–4) were obtained through factor analysis and assessment of internal consistency data with the goal of obtaining a smaller scale that was as informative and reliable as the UHDRS-TMS.[4] Internal consistency has been reported to be very good in manifest HD, with Cronbach α values of 0.97 for the TMS1, 0.92 and 0.93 for the TMS2, 0.97 and 0.96 for the TMS3, and 0.95 and 0.96 for the TMS4.[6] Test-retest reliability has also been shown to be very good (range, 0.86–0.93), although correlation coefficients were used, and the 2 samples of patients with manifest HD were small (n = 32 and n = 35).[6] The UHDRS-TMS4 also was considered sensitive to change over time.[22] The original developers of the reduced versions of the UHDRS-TMS considered the UHDRS-TMS4 to be the most suitable for evaluating disease progression, because it is a short and practical test that describes overall motor function and, most important, does so independent of cognitive loading.[4]

Recommendation

The UHDRS-TMS4 is "suggested" for the assessment of severity of motor signs in HD. The UHDRS-TMS4 warrants further clinimetric development, namely, inter-rater reliability and construct validity testing.

Quantified Neurological Examination

The Quantified Neurological Examination (QNE) is a clinician-rated scale that was first described in 1983[23] and was specifically developed for use in HD. The QNE consists of 48 items with a maximum possible score of 129 points. Factor analysis revealed 2 subscales of highly internally correlated items: a chorea scale (a measure of involuntary movement) and a motor impairment scale (MIS) (a measure of abnormalities of voluntary movement).[23,24] An eye-movement subscale is also reported.[25] The QNE is considered more accurate for ascertaining HD severity as opposed to screening for involuntary movements.[23,24] It relies on objective examination by the rating clinician. Although the QNE has been used in multiple groups, the existing clinimetric data were generated strictly by the original developers.[23–25] The reported test-retest and inter-rater reliabilities have been very good, although correlation coefficients were used (values ranged between 0.89 and 0.95, respectively).[23] Construct validity of the QNE, and particularly of the MIS, has been demonstrated with the Huntington's Disease Activities of Daily Living scale (correlation coefficients: QNE total score, 0.59[26]; MIS, 0.70[26,27]; chorea scale, 0.40[26]) and the UHDRS-Total Functional Capacity (correlation coefficients: QNE total score, −0.74; MIS, −0.70; chorea scale, −0.49).[26] Data from observational studies and negative clinical trials in HD suggest that the QNE has the ability to track change over time.[28,29]

Recommendation

The QNE is "suggested" for the assessment of severity of motor signs in HD. The QNE was developed by a single group, and most (but not all) studies in HD using the QNE have been authored by the original developing group. The committee found that clinimetric development was not sufficient to warrant a classification of "recommended," because there is a lack of measures like internal consistency and reproducibility of core clinimetric characteristics by groups other than the developers. In addition, the use of the QNE has been vastly replaced by the UHDRS-TMS.

Marsden and Quinn Chorea Severity Scale

The Marsden and Quinn Chorea Severity Scale is a clinician-rated scale derived from an unpublished chorea severity scale by Fahn and Lhermitte and was developed by Marsden and Quinn to provide a reasonable estimate of current severity of chorea using an expert-based approach.[30] It takes approximately 10 minutes to complete and consists of 5 items: severity of chorea, which is rated separately in different body parts, and items for speech, gait, postural stability, and manual dexterity.[30] It is considered to be applicable across all stages of HD, because it relies on an objective evaluation of chorea by the examiner. No clinimetric data are available on its reliability or validity, but it has been shown to be sensitive to change with treatment in clinical trials assessing pharmacological interventions for the treatment of chorea.[31–33]

Recommendation

The Marsden and Quinn Chorea Severity Scale is "suggested" for the assessment of severity of chorea in HD. There is a complete lack of core clinimetric data for the Marsden and Quinn Chorea Severity Scale, but this scale has been used by at least 2 independent research groups, which have provided information about its responsiveness to treatment for chorea.

Abnormal Involuntary Movement Scale

The Abnormal Involuntary Movement Scale (AIMS) was originally designed to measure tardive dyskinesia[34] but has been used in various randomized controlled trials in HD.[9,31,35–37] The scale consists of 12 items, which rate involuntary movements in 7 body areas (face, lips, jaw, tongue, upper extremities, lower extremities, and trunk) as well as the overall severity, incapacitation, patient's level of awareness of the movements, and distress associated with the involuntary movements. The AIMS is a relatively quick (15 minutes), practical, and easy to use clinician-rated scale. The AIMS is less applicable in patients with premanifest HD, in whom chorea is absent, and in later stages of HD, when patients may not be able to follow the AIMS protocol, which requires the patient to first sit quietly at rest before performing selected motor tasks.[34,38] No clinimetric data on reliability or validity of the AIMS are available in HD. The AIMS has been used in several clinical trials targeting the treatment of chorea in HD and has been shown to be sensitive to change after treatment.[9,31,35,36]Poor inter-rater reliability has been reported for the motor subscore when used by nonexperienced users assessing patients with tardive dyskinesia, thereby suggesting that training is also required to use the scale appropriately in HD.[39]

Recommendation

The AIMS is "suggested" for assessing the severity of chorea/dystonia in HD. Although core clinimetric assessments are not available in HD, the AIMS has been used in multiple clinical trials, with data from its use providing information about sensitivity to change after treatment.

Discussion

The current review of motor rating scales in HD concludes that the UHDRS-TMS is the only rating scale that can be "recommended" to measure the severity of motor signs in HD. Nevertheless, it still requires further clinimetric development. For example, it is our view that factor analysis could be studied more extensively with available data from large HD cohorts, such as PREDICT-HD, COHORT, REGISTRY, or TRACK-HD. The same would apply to responsiveness testing. In addition, the lack of determination of minimal clinical significant changes for the UHDRS-TMS was identified as an important gap, but the subcommittee also recognizes that this clinimetric information is lacking in most (if not all) clinical rating scales in HD. As a multi-item scale, the UHDRS-TMS includes various features of the motor domain in HD; as such, an observed change may be difficult to interpret in a longitudinal assessment. Available clinimetric data show that items assessed by the UHDRS-TMS have variable weights at different HD stages: chorea is predominant in earlier stages of manifest HD, tends to plateau, and fades later in the natural history of the disease; whereas parkinsonian features become progressively more severe and are more clinically significant in later stages of the disease.[23] Therefore, future research should seek to determine the magnitude of a significant (or important) change in the UHDRS-TMS score at different disease stages.

An important aspect of discussion is the use of a motor rating scale that attempts to cover all motor domains in HD versus a scale that specifically targets a single motor feature in HD, such as chorea. We consider that the objectives for which a scale is being used largely determine the choice of 1 solution or the other. For example, a multi-item scale definitely facilitates data collection on multiple motor features in HD, which is helpful for observational studies focused on the natural history of HD. In clinical trials of interventions that attempt to target various motor features in HD, a multi-domain scale can assess the differential effect of a novel treatment on these HD motor features, allowing for a more comprehensive evaluation of the therapeutic effects of a novel treatment. On the other hand, a

scale that specifically targets a single motor feature in HD and has been validated for this purpose will be better in assessing for a specific symptomatic treatment indication, although not assessing other motor domains may overlook other therapeutic benefits or side effects.

Reasonable numbers of scales have been developed specifically for HD that measure motor signs or symptoms. The UHDRS-TMS, its reduced versions, the QNE, and the Marsden and Quinn Chorea Severity Scale support this observation. We did not identify a motor rating scale that could be recommended for screening purposes or that was fully tested to assess change over time. It is our impression that the currently available clinical rating scales may serve these purposes in the future, but only after more comprehensive clinimetric development is completed.

Another important discussion in the assessment of motor domains in HD is the need to integrate the aspect of impairment of motor performance. We have reviewed scales that measure motor performance testing or the impact of motor signs/symptoms in daily functioning in a separate critique examining functional rating scales in HD. These measurement tools, which capture the "functional" impact of motor impairment, have gained further recognition and attention by regulatory agencies.[40]

An area of growing interest and undelivered potential in HD (and in movement disorders at large) is the use of motor quantification methods with novel technologies, including wearable devices known as "wearables," but a critical appraisal of these devices was beyond the scope of the current review.

This critique leads to the main conclusion that the clinimetric properties of the UHDRS-TMS are sufficiently characterized and that the scale performs well for it to be an effective research and clinical practice tool for assessing HD gene carriers who have clear motor symptoms and for characterizing these in terms of severity. For those individuals who have subtle manifestations, the UHDRS-TMS is unlikely to be the ideal instrument, either because the relevant motor features need better representation or because the scaling properties of existing items are not sufficient to capture the different manifestations. Together, these findings suggest that, for premanifest and/or prodromal stages of HD, a dedicated instrument would need to be developed.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Flowchart of the review: 27 rating scales initially identified

Table S2. Recommended: The Unified Huntington's Disease Rating Scale '99 (UHDRS) motor section

Table S3. Suggested: Quantified Neurological Examination (QNE)

Table S4. Suggested: Marsden and Quinn Chorea Severity Scale

Table S5. Suggested: Abnormal Involuntary Movement Scale (AIMS)

Table S6. Suggested with caveats: Rockland-Simpson Dyskinesia Rating Scale (RSDRS)

Table S7. Listed: Kartzinel, Hung, and Carne Rating Scale