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Objective assessment of gait and posture in premanifest and manifest Huntington disease — A multi-center study

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ABSTRACT

Background: Deficits in posture and gait are known to contribute to the complex motor phenotype of Huntington disease (HD). Objective and quantitative measures of posture and gait provided by posturography and GAITRite® assessments may supplement categorical rating scales such as the UHDRS-TMS and increase power and sensitivity of clinical trials.

Objectives: To investigate whether posturography and GAITRite® measures reveal (1) changes in manifest or premanifest HD mutation-carriers, (2) a correlation to the UHDRS-TMS and functional measures in manifest HD, and (3) a correlation to the disease-burden-score (based on CAG-repeat-length and age).

Methods: Posturography and GAITRite® were applied in premanifest (n = 26) and manifest HD gene-mutation-carriers (n = 40) in different paradigms compared to age-matched controls (n = 30) in a cross-sectional multi-site study conducted in three centers. Subjects were assessed clinically with the UHDRS Total-Motor-Score, Total-Functional-Capacity and Functional-Assessment-Scale.

Results: Several posturography measures were able to discriminate between controls, premanifest, and manifest mutation-carriers in both conditions assessed. Only one GAITRite® measure separated controls and premanifest participants, while discrimination between controls and manifest same as between premanifest and manifest participants was possible in several measures. Correlation with all clinical measures was seen in only one measure per device while correlations to the disease-burden-score seen in posturography only.

Conclusion: Overall the results suggests that posturography detects alterations in premanifest and manifest mutation-carriers more reliably than GAITRite® measures. Correlations with clinical assessment scores are limited; correlation with disease-burden-score is seen in posturography only. Data acquisition and analysis was easier with posturography than GAITRite® assessments in out-patient settings.

1. Introduction

Huntington disease (HD) is an autosomal-dominant progressive neurodegenerative disease characterized by a variety of motor, cognitive, behavioural, and psychiatric signs and symptoms [1]. Motor symptoms range from predominantly hyperkinetic choreatic movements in early and mid stages to complex deficits including bradykinesia, rigidity, and dystonia in more advanced stages.

Impairments in motor coordination were detected, e.g., in finger movements, [2–4] grasping, [5–8] balance [9] and gait [10]. Early motor signs and symptoms are often subtle and may not be captured well by categorical clinical rating scale such as the Unified-Huntington's-Disease-Rating-Scale Total-Motor-Score (UHDRS-TMS). In addition, this scale may be affected by rater biases, intra- and inter-rater variability, and placebo effects [11,12]. Nevertheless, the UHDRS-TMS or subscales frequently serve as endpoint in clinical trials in HD e.g. [13–16], and are a core component of observational studies [16–20]. Thus, more sensitive and reliable assessments are desirable, particularly

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for proof-of-concept studies in smaller patient cohorts. An instrumented objective and quantitative assessment of motor deficits may provide a higher sensitivity, reduce variability and placebo effects [12] and may even allow for detection and follow-up of motor signs in prodromal and premanifest HD [17], e.g. [21–23].

HD inevitably results in visible deficits in gait [24] and posture [25] in symptomatic patients. Measurable decrease in gait speed, cadence, and an increase in stride time measured by a video motion analysis system have also been detected in early-stage HD patients [26]. Postural instability was assessed quantitatively and objectively using posturography (PG) in a cross-sectional study in symptomatic patients with HD [27] and subjects at-risk for HD [28]. It was also shown that deficits in postural stability in symptomatic patients correlated to the UHDRS-TMS and the Functional Assessment Scale (FA) of the UHDRS [9]. Gait impairment in HD was objectively quantified using the force sensor equipped mat GAITRite® (GR) providing data on inter-step time, stride DISTANCE, and other gait measures in symptomatic HD patients [29] and premanifest gene carriers [10,30].

Objective measures of motor dysfunction provided by techniques such as PG and the GR may potentially supplement established scales in clinical trials [31]. Applied in multicenter settings and follow-up studies they could reduce costs and patient burden in trials [12]. However, to date the sensitivity of both devices to detect motor deficits and correlations to clinical symptoms has never been compared head-to-head in manifest and premanifest HD gene carriers.

We therefore decided to compare both PG and GR head-to-head in a prospective multi-site study, hypothesizing that motor deficits in posture and gait as detected by both devices are (1) correlated to the severity of motor phenotype as assessed in the UHDRS-TMS in symptomatic HD, (2) detectable in premanifest mutation-carriers, and (3) correlate to the genotype as assessed by the disease burden score (DBS, based on CAG-repeat length and age) [32]. In addition, we aimed to explore the correlation of the PG and GR measures with functional scales commonly used in HD.

2. Methods

2.1. Subjects

40 subjects with symptomatic HD (24 females and 16 males) and 26 premanifest mutation-carriers (14 females and 12 males) – characteristics see Table 1, and 30 healthy and age matched control subjects (19 females and 11 males, mean age 38.6 years, range 23–60 years) participated in the study after giving their informed consent in accordance with the declaration of Helsinki. The study was approved by the Institutional Review Boards of the Universities of Münster, Bochum, and Ulm. Subjects were naïve with respect to the aims of the study. CAG-expansion was known from all subjects in the premanifest and symptomatic HD group except one. Each subject was clinically assessed with the UHDRS-TMS [11], Total Functional Capacity (TFC), and Functional Assessment Scale (FA) by a physician experienced in the care of patients with HD and the application of the scales and certified by the European Huntington Disease Network (EHDN) UHDRS-TMS online certification [33]. Mutation-carriers with a UHDRS-TMS ≤ 4 and UHDRS diagnostic confidence level < 4 were assigned to the premanifest group [34]. Exclusion criteria for subject recruitment were: (1) other co-existing chronic neurological diseases, (2) arthritis or orthopedic problems, (3) major depression, (4) active psychosis (assessed by Hamilton Depression Scale and Brief Psychiatric Rating Scale), and (5) juvenile HD. Neurological examination was normal in all controls and there was no history of neurological or psychiatric disorders or substance abuse.

2.2. Experimental setup & task

2.2.1. Gait analysis with GAITRite®

The *GAITRite®* system (CIR-Systems, Franklin, NJ, USA; www.GAITRite®.com) – see Fig. 1a – is an electronic walkway measuring temporal (timing) and spatial (distance) gait parameters (temporospatial) by means of sensor pads encapsuled in a carpet providing an active assessment area of 61 cm width and 427 cm DISTANCE; it contains a grid of 48 × 336 sensors placed on pads of 0.5 inch (1.27 cm) diameter, totaling 16,128 sensors. The mat is placed evenly for assessment, e.g., in a hallway. As the patient ambulates across the mat, the system continuously scans the sensors to detect objects with a scan rate of 60 Hz. The area of the object is determined by the number of sensors activated, the distance between these sensors and the time of activation and deactivation is used to assess the gait dynamics. The walkway transfers the information to the computer via a USB interface cable. The application software controls the walkway, processes the raw data into footfall patterns – see Fig. 1b, and computes the temporospatial measures (VELOCITY, STRIDE DISTANCE, DOUBLE SUPPORT). The software's relational database then stores tests individually under each subject's indentifier. In addition, the measure STRIDE LENGTH COEFFICIENT OF VARIABILITY was computed with Windows® Excel 2003 by the formula: $Coeff_{SLV}$ = (Stride Length Variability Standard Deviation/Mean Value) ×100.

Two tasks are performed, after a cueing tone patients walk across the mat at (1) NORMAL and (2) FAST speed (not running). Four trials were performed for each task, each taking approx. 10–20 s.

2.2.2. Posturography with force plate

The *Force Plate* (SATEL, Blagnac, France, www.satel-posture.com) – see Fig. 2a – was a 48 × 48 cm force sensor equipped metal podium connected to a Windows XP® computer by serial cable. Sensors in the plate scanned at a rate of 40 Hz for 25 s per trial. Results were stored on the computer after processing with the application software. Each assessment began with an automated calibration of the plate. The subject then mounted the plate barefoot in a standardized position in the center of the device. During the assessment, the subject was instructed to stand as still as possible, while temporospatial deviations of the center of

Table 1
SubjectCharacteristics.

Measure	premanifest HD					manifest HD				
	MEAN	± SD	MEDIAN)	MAX	MIN	MEAN	± SD	MEDIAN	MAX	MIN
Age	37.9	11.1	36	67	22	47.7	9.9	48	70	25
CAG-Repeat	41.6	2.3	42	49	39	44.1	2.9	44	53	39
UHDRS-TMS	1	1.4	0	4	0	33.6	16.7	34	59	5
UHDRS-TFC	12.96	0.2	13	13	12	8.9	3.5	10	14	2
UHDRS-FA	25	0	25	25	25	19.1	6.3	23	25	6
HAMD	1.6	3.6	0	17	0	6.3	6.4	4	26	0
BPRS	0.3	1.2	0	6	0	0.9	1.4	0	4	0

BPRS = Brief Psychiatric Rating Scale; FA = Functional Assessment Scale; HAMD = Hamilton Depression Scale; MAX = maximum value; MEAN = average; MEDIAN = median; MIN = minimum value; ± SD = standard deviation; TFC = Total Functional Capacity; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale