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Insights into gait disorders: Walking variability using phase plot analysis, Huntington's disease

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ABSTRACT

Huntington's disease (HD) is a progressive inherited neurodegenerative disorder. Identifying sensitive methodologies to quantitatively measure early motor changes have been difficult to develop. This exploratory observational study investigated gait variability and symmetry in HD using phase plot analysis. We measured the walking of 22 controls and 35 HD gene carriers (7 premanifest (PreHD)), 16 early/mid (HD1) and 12 late stage (HD2) in Oxford and Cardiff, UK. The unified Huntington's disease rating scale-total motor scores (UHDRS-TMS) and disease burden scores (DBS) were used to quantify disease severity. Data was collected during a clinical walk test (8.8 or 10 m) using an inertial measurement unit attached to the trunk. The 6 middle strides were used to calculate gait variability determined by spatiotemporal parameters (co-efficient of variation (CoV)) and phase plot analysis. Phase plots considered the variability in consecutive wave forms from vertical movement and were quantified by SD_A (spatiotemporal variability), SD_B (temporal variability), ratio $\forall$ (ratio SD_A:SD_B) and Δangleβ (symmetry). Step time CoV was greater in manifest HD ($p < 0.01$, both manifest groups) than controls, as was stride length CoV for HD2 ($p < 0.01$). No differences were found in spatiotemporal variability between PreHD and controls ($p > 0.05$). Phase plot analysis identified differences between manifest HD and controls for SD_B, Ratio $\forall$ and Δangle (all $p < 0.01$, both manifest groups). Furthermore Ratio $\forall$ was smaller in PreHD compared with controls ($p < 0.01$). Ratio $\forall$ also produced the strongest correlation with UHDRS-TMS ($r = -0.61$, $p < 0.01$) and was correlated with DBS ($r = -0.42$, $p = 0.02$). Phase plot analysis may be a sensitive method of detecting gait changes in HD and can be performed quickly during clinical walking tests.

1. Introduction

Huntington's disease (HD) is a dominantly inherited progressive neurodegenerative condition caused by a cytosine–adenine–guanine (CAG) repeat mutation in the *HTT* gene. It predominantly affects the brain, causing dysfunction and death of medium spiny striatal projection neurons and thus disruption of corticostriatal pathways with resultant impairment of cognition, motor function, and behaviour [1]. HD is a monogenic, fully penetrant disorder and characterised by a long premanifest stage which presents the opportunity to use early therapeutic interventions prior to symptom onset [2]. There is an urgent need to develop biomarkers and outcome measures for therapeutic trials of potential disease-modifying therapies currently under development [3]. Recently Tabrizi et al. [2] reported the 24-month observational data from TRACK-HD identifying potential endpoints for clinical trials in premanifest and early HD. However, they failed to find a strong candidate quantitative motor measure, although the Unified Huntington's disease rating scale (UHDRS) total motor score (TMS) confirmed that early motor changes were present. Whilst the UHDRS-TMS appears to be sensitive

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there remains a need to identify further markers to quantify motor symptoms in premanifest and early HD [2].

New technologies have allowed the development of accessible methods of analysing gait. Small inertial measurement units (IMU) can be simply attached to the lower back to track projected centre of mass (CoM) movement during walking [4], providing a reference to indicate global gait quality [5]. An advantage of analysing gait in this way is that the entire sinusoidal waveform produced by of trunk movement (reflecting vertical movement of the CoM) can be analysed rather than just obtaining single values for the spatiotemporal events that occur during the gait cycle.

When measuring multiple gait cycles, variability in spatiotemporal measures has been shown to be sensitive in detecting early [6,7] and longitudinal gait changes [8] in HD. Considering that spatiotemporal events are reflected in the CoM displacement [9] walking variability may be observable in the CoM signal. Indeed the cyclic nature of walking lends itself to measuring gait variability using the entire CoM sinusoidal wave form. The differences between consecutive cycles, the self-similarity of the periodic function, can be investigated via non-linear methods by plotting the waveform against itself with a 360° phase shift (phase plot analysis). This can be used to quantify the variability and symmetry of the CoM wave form. We have previously explored CoM movement during walking using this method and found that Parkinsonian and healthy walking could be differentiated during a 10-m walk test using phase plot analysis despite no detectible differences in standard spatiotemporal parameters [10].

This study explores the use of phase plot analyses to quantify motor changes in walking in HD.

2. Methods

2.1. Participants

Individuals with CAG repeat mutation in the *HTT* gene, who attended the HD clinics at the Oxford University Hospitals, UK or the University Hospital of Wales, UK between July 2009 and December 2011, were offered participation in a provisional exploratory observational study in accordance with local research ethics committee permissions (10/WSE02/74; 09/WSE02/24). The participants in this study represent a convenience sample. All participants provided informed consent prior to participation. Inclusion criteria were a genetically confirmed diagnosis of HD, age 18 or over, capacity for informed consent, no major concurrent psychiatric illness, ability to walk independently as primary means of mobility, and to have maintained a stable medical regime for 4 weeks prior to the assessment. Exclusion criteria were a history of prior neurological condition or orthopaedic condition that independently limited mobility. A healthy control group was also recruited of similar age and gender to the HD participants from the general public. The control participants were aged 18 or over and free from peripheral injury or other condition that meant they were unable to walk without assistive devices. HD gene carriers were stratified into premanifest (PreHD), early/mid manifest (HD1) and late manifest (HD2). PreHD were defined by an UHDRS-TMS of ≤ 5 [11], HD1 by an UHDRS-TMS of >5 and UHDRS-Total Functional Capacity (TFC) of 7–13 and HD2 by an UHDRS-TFC of 0–6 [12].

2.2. Assessments

Demographic data including age (years), gender, height and weight and leg length was obtained and are summarised in Table 1. Clinical features of HD were quantified using the UDHRS. The UHDRS comprises a series of clinical scales to assess motor function, cognitive function, behavioural abnormalities, and functional capacity. The UHDRS-TMS assesses a range of voluntary

Table 1
Descriptive and clinical characteristics of participants.

Group	*n* (male:female)	Age (years)	Weight (kg)	Height (m)	Leg length (m)	BMI	UHDRS TFC[a]	UHDRS TMS[a]	UHDRS FAS[a]	UHDRS independence scale[a]	CAG	DBS[a]
Control	22 (11:11)	46 ± 10	76.2 ± 15.2	1.70 ± 0.10	0.91 ± 0.06	26.1 ± 3.6	NA	NA	NA	NA	NA	NA
PreHD	7 (2:5)	48 ± 16	76.6 ± 29.8	1.69 ± 0.11	0.93 ± 0.07	26.0 ± 6.4	13 (13–13)	1 (0–4)	25 (25–25)	100 (100–100)	41 ± 3	260.3 ± 76.4
HD1	16 (9:9)	47 ± 10	75.7 ± 10.6	1.69 ± 0.10	0.92 ± 0.06	26.5 ± 6.4	9 (7–13)	28.5 (11–73)	22 (15–25)	80 (65–100)	45 ± 3	411.0 ± 87.1
HD2	12 (9:3)	50 ± 14	79.2 ± 12.1	1.69 ± 0.07	0.90 ± 0.03	28.1 ± 6.2	5 (4–6)	59.5 (17–78)	17 (10–21)	70 (60–95)	47 ± 7	506.7 ± 137.7

Results displayed as mean ± SD and median (range).
BMI, body mass index (BMI = Weight × (Height^2)); UHDRS, unified Huntington's disease rating scale; TFC, total functional capacity; TMS, total motor score; FAS, functional assessment scale; CAG, cytosine–adenine–guanine repeat length; DBS, disease burden score; NA, not applicable.
[a] All HD groups significantly different from each other ($p < 0.05$).