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Factors that contribute to balance and mobility impairments in individuals with Huntington's disease

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ABSTRACT

Mobility and balance problems are common and often debilitating features of Huntington's disease (HD). In this exploratory study we aimed to investigate the influence of disease severity, severity of motor deficits, lower limb muscle strength, cognition, executive function, lean muscle mass and reactivity on mobility and balance.

Twenty-two individuals with HD were recruited from the North Metropolitan Area Mental Health Service, Perth, Australia. Pertinent demographic, genetic and disease progression information was recorded prior to testing. Balance was assessed using dynamic and static balance tasks. Mobility was assessed using self-paced and fast-paced mobility measures. Cognitive and executive measures were used to assess verbal learning and memory, information processing speed, attention, response inhibition and cognitive flexibility. Lower limb muscle strength was evaluated by maximal isokinetic and isometric voluntary contractions. Lean tissue mass was quantified using Dual-energy X-ray absorptiometry. Reactivity was measured using Moyart equipment.

Univariate and multivariate linear regression statistical models were used to examine the influence of these measures on mobility and balance. Univariate analyses showed that disease severity as well as measures of information processing speed, attention, cognitive flexibility, response inhibition and lower limb strength, were strongly related with mobility and balance. Additionally multivariate analyses showed that disease severity, cognitive flexibility and knee flexion strength together were better able to explain mobility and balance performance than any single measure (50–85%).

In conclusion, our preliminary results suggest that as well as disease severity, cognitive and executive impairment and reduced lower limb strength contribute significantly to mobility and balance problems.

Introduction

Problems with balance and mobility are commonly reported by individuals suffering with HD. Problems occur early in the disease course and worsen with disease progression [1]. Impairments in balance and mobility often predict nursing home placement, increase the likelihood for falls and can severely impact on health related quality of life [2,3].

There are no clinically proven treatment strategies for addressing balance and mobility problems in people with HD. Previous studies examining mobility and balance in people with HD have documented decreases in gait velocity and stride length, increases in stride-to-stride variability, double support time and step time, and increased postural sway [4–10]. While providing a vivid description of mobility and balance issues, previous studies have failed to investigate clinical features that contribute to mobility and balance problems in HD.

Studies in people with Parkinson's disease (PD) have reported strong associations between muscle power and strength and performance on balance and mobility tasks [11–13]. Task dependent relationships between cognition and mobility and balance have also been documented in PD [12]. Similar associations have been reported in people with multiple sclerosis (MS) [14–17]. In the elderly, age related losses of lean tissue have been reported to strongly predict mobility and balance problems [18]. Individuals with HD, in addition to displaying movement

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symptoms, exhibit progressive cognitive and executive impairment [19–23] as well as skeletal muscle atrophy throughout the disease course [24,25], which may similarly adversely impact on balance and mobility.

Emerging evidence suggests that in HD, reduced muscle strength, cognitive and executive problems as well as skeletal muscle atrophy are remediable to interdisciplinary rehabilitation approaches [25–27]. This exploratory study therefore aimed to investigate the influence of motor, cognitive, executive and body composition features of the disease on mobility and balance performance in people with HD as a better understanding of the contribution of these deficits to balance and mobility may lead to improved therapies in HD.

Materials and methods

Ethics approval

This study was approved by the Human Research Ethics Committee at Edith Cowan University and the North Metropolitan Area Mental Health Service (NMAMHS) Human Research Ethics Committee. All participants provided written informed consent.

Participants

Sixty-two potential participants were identified using the Neuroscience Unit database of the NMAMHS. Participants were only included if they had received a positive genetic test, were formally diagnosed as symptomatic (Unified Huntington's Disease Rating Scale Total Motor Score [UHDRS-TMS] ≥ 5), and had the ability to follow verbal or written instruction. Participants were not included if they had recent substance abuse, an unstable psychiatric state, confounding neurological condition or concomitant physical injury.

Study procedures

Participants were evaluated over two weekends at Edith Cowan University using a variety of mobility and balance tasks as well as cognitive, executive, lower limb muscle strength, lean tissue mass and reactivity measures. All assessments were performed by accredited independent examiners.

Outcome measures

Dynamic and static balance was examined using the berg balance scale (BBS), sensory organisation test (SOT) and the repeated sit to stand test (RSST). Mobility over short and long distances was quantified using the timed walk test (TWT) and the six minute walk test (6MWT) [28]. These measures have previously been demonstrated to be reliable in individuals with HD [28,29].

Predictor measures

Disease severity and severity of motor abnormalities were measured using the disease burden score and the UHDRS-TMS. Cognition and executive function was examined using a variety of clinically validated measures. The Hopkins Verbal Learning Test-Revised (HVLT-R) was used to measure verbal learning and memory [25,30]. Information processing speed and attention were examined using the Symbol Digit Modalities Test (SDMT) [25,31]. Response inhibition and cognitive flexibility were examined using the Delis-Kaplan Executive Function System (D-KEFS) Colour Word Interference Test (CWIT) and Trail Making Trials (TMT) [25]. Reactivity was measured using a visual response task. Dual-energy X-ray absorptiometry (DEXA; Hologic Discovery A) was used to quantify lean tissue mass (g) [25]. Lower limb muscle strength was quantified using a maximal voluntary isometric and isokinetic knee flexion and extension contractions with automated dynamometry (Biodex, System 3, USA). Isokinetic knee extension and flexion strength was examined using $180^\circ\,s^{-1}$ (fast) and $30^\circ\,s^{-1}$ (slow) maximum voluntary contraction (MVC) test protocols. Isometric knee extension and flexion strength were also measured at 60° flexion. Individuals performed three maximal voluntary contractions for each strength protocol.

Statistical analysis

Data are presented as mean, range and standard deviation (SD). Associations between balance and mobility tasks (outcome variables), disease severity, severity of motor abnormalities and measures of cognition, executive function, lower limb strength, lean tissue mass and reactivity (predictor variables) were determined using univariate linear regression analysis. Associations between multiple predictor variables and balance and mobility were then determined using multivariate linear regression. The results of the univariate linear regression analysis showed that measures of disease severity, attention, information processing speed, cognitive flexibility and response inhibition associated strongly with balance and mobility tasks. These predictor variables were entered into a multivariate linear regression model and assessed for association with each of the mobility and balance tasks. Backward selection estimation was then used to obtain the most significant multivariate model. Statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using STATA version 9.1.

Results

Of the sixty-two potential participants, twenty-two individuals agreed to voluntarily participate in the study (Table 1.) Of these, 16 were taking antidepressants, 12 anti-psychotics and 5 anti-choreic medications (Table 1). Demographic, disease severity, severity of motor abnormalities, cognition, executive function, lower limb strength, lean tissue mass, reactivity, mobility and balance data are displayed in Tables 1 and 2.

Balance

Univariate analyses revealed significant associations between disease severity and performance on balance tasks (18–50.0% for disease burden score). Moreover, measures of information processing speed, attention, cognitive flexibility, response inhibition and lower limb strength were significantly associated with performance on balance tasks (20.3–27% for correct oral, 18.2–53.0% for word reading, 26.3–49.5% for motor speed, 24.5–42.7% for 60° MVC knee flexion; Tables A.1–A.3). Task dependent associations between measures of verbal learning and memory and performance on the RSST task were also found (total recall 21.3%). Lean tissue mass, reactivity and severity of motor abnormalities were found not to be related to balance task performance (Tables A.1–A.3).

Table 1
Participant characteristics.

Variables	Mean (SD) ($n = 22$)	Range
Age (years)	50.85 ± 9.24	30.3–70
Disease duration	3.95 ± 4.26	0.3–17.3
CAG (n)	44.22 ± 2.99	39–51
Disease burden score	427.22 ± 118.05	269.5–596
UHDRS-Total Motor Score	26.45 ± 12.41	5–45

Table 2
Study participant performance on outcome measures.

Study assessments	Mean (SD)	Range
Predictor variables		
Cognition assessments		
SDMT		
Correct written	26.33 ± 10.57	10.00–48.00
Incorrect written	1.66 ± 1.95	0.00–6.00
Correct oral	29.71 ± 13.40	8.00–60.00
Incorrect oral	1.85 ± 2.34	0.00–7.00
HVLT-R		
Total recall	16.52 ± 6.20	4.00–30.00
Delayed recall	5.13 ± 2.35	1.00–9.00
Retention	77.00 ± 22.59	33.00–129.00
Recognition discrimination index	8.00 ± 3.08	2.00–15.00
D-KEFS TMT		
Visual scanning	35.42 ± 15.83	16.00–70.00
Number sequencing	59.57 ± 21.84	33.00–124.00
Letter sequencing	79.10 ± 55.56	31.00–234.00
Number–letter sequencing	142.00 ± 54.24	61.00–239.00
Motor speed	65.44 ± 35.16	18.00–147.00
D-KEFS CWIT		
Colour naming	44.05 ± 15.72	22.00–78.00
Word reading	35.14 ± 13.81	20.00–73.00
Inhibition	89.42 ± 33.52	40.00–186.00
Lower limb strength measures		
30° s^{-1} MVC knee extension	127.23 ± 54.36	40.80–217.10
180° s^{-1} MVC knee extension	71.05 ± 29.92	20.90–128.45
30° s^{-1} MVC knee flexion	71.88 ± 32.44	15.60–138.95
180° s^{-1} MVC knee flexion	50.19 ± 19.33	14.30–96.00
60° MVC knee extension	157.30 ± 49.06	71.10–238.95
60° MVC knee flexion	65.46 ± 18.73	14.80–100.25
Body composition assessment		
Lean tissue mass	52224.47 ± 10332.29	34362.20–68907.30
Reactivity assessments		
Visual reaction time (DOM)	0.69 ± 0.24	0.34–1.20
Visual reaction time (NON)	0.67 ± 0.25	0.26–1.21
Outcome variables		
Balance assessments		
SOT	54.04 ± 15.63	22.00–80.00
BBS	46.59 ± 7.83	26.00–56.00
RSST	28.62 ± 12.76	12.00–64.00
Mobility assessments		
TWT (fast-paced)	6.17 ± 2.81	3.08–16.72
TWT (self-paced)	8.10 ± 2.63	5.90–17.18
6MWT	466.19 ± 127.37	87.00–630.00

DOM, dominant hand; NON, non-dominant hand.

Multivariate analyses showed that performance on the BBS was best explained by disease severity (disease burden score explained 57%; Table A.7). For the SOT, performance variability was best explained by disease severity and cognitive flexibility measures (disease burden score and motor speed together explained 50% of variability; Table A.7). Performance variability on the RSST was best explained by measures of cognitive flexibility and knee flexion muscle strength (motor speed and 60° MVC knee flexion strength together explained 72%; Table A.7)

Mobility

Univariate analyses showed significant associations between disease severity and performance of mobility tasks (disease burden score 43–50%). Measures of attention, information processing speed, cognitive flexibility, response inhibition and lower limb strength measures were also associated with mobility task performance (correct oral 20–40.1%, word reading 34.1–52.2%, motor speed 26.7–52.8%, 60° MVC knee flexion strength 43–60%; Tables A.4–A.6). Task dependent associations between verbal learning and memory and mobility task performance were also evident (total recall, 19.5%; Tables A.4–A.6). There was no evidence of associations between lean tissue mass, reactivity or severity of motor abnormalities and performance on mobility tasks (Tables A.4–A.6).

Multivariate analyses revealed that when measures were collectively considered, disease severity, cognitive flexibility and knee flexion strength measures explained a significantly greater proportion of performance variability on mobility tasks than any single measure (TWT-SP 85%, TWT-FP 72%, 6MWT 85%; Table A.7).

Discussion

This study found that disease severity, lower limb muscle strength, cognition and executive function significantly influenced performance on balance and mobility tasks, while reactivity and lean tissue mass did not. Furthermore, this study showed that when all measures were collectively considered, the factors most critically related to performance on balance and mobility tasks were disease severity, cognitive flexibility and knee flexion strength, and together these measures better explained balance and mobility performance than any single measure.

An important finding of this study was that cognition and executive function significantly influenced performance on balance and mobility tasks. Similar findings have been found in people suffering from PD [12,32,33] and mild cognitive impairment (MCI) [34]. Paul et al. [12,32] in two recent studies showed that executive function and cognition significantly influenced balance and falls in people with PD. Persad et al. [34] in a similar study found that cognition and executive function were strongly related to balance and mobility in people with MCI. These findings highlight that deterioration of cognitive and executive function adversely impacts upon balance and mobility in people with neurodegenerative diseases.

The relationship of lower limb strength with balance and mobility task performance was not unexpected. Interestingly though, we found that relationships were often dependent on the muscle group involved and the type of contraction performed, with the 60° MVC knee flexion measure demonstrating significant association with all balance and mobility tasks. Both 30° s^{-1} MVC knee flexion and 180° s^{-1} MVC knee flexion measures similarly demonstrated strong associations with performance on mobility tasks but not balance tasks. Broekmans et al. [35] in a similar study found knee flexion strength to strongly predict walking capacity in people with MS. Knee flexor involvement during stabilisation and mobility tasks in healthy individuals is well established [36–38], and likely explains our findings. Multidisciplinary interventions have been shown to improve lower limb strength and perception of balance in people with HD [25], therefore mobility and balance problems may be amenable to such interventions.

As expected, a strong relationship was observed between disease severity and performance on balance and mobility tasks, indicating a significant contribution of HD progression to movement disability. Of interest, is the finding that severity of motor abnormalities, as measured by the UHDRS-TMS, was not significantly associated with performance on balance and mobility tasks. This finding has important clinical implications for the assessment of balance and mobility in HD. It illuminates the importance of identifying specific measures to supplement the UHDRS-TMS that can more sensitively quantify balance and mobility decrements.

Lean tissue mass and reactivity demonstrated negligible associations with mobility and balance. This was an unexpected finding, considering that studies in PD have reported reactivity and lean muscle mass to be important clinical determinants of balance and mobility performance [12,32,39]. Discrepancies between findings are likely due to pathological and clinical differences between PD and HD [40,41], as well as methodological and sample size differences between the studies.

Our findings result from a relatively small sample of individuals with manifest HD, most of whom were taking medication, as such our findings should be interpreted with a degree of caution.

Conclusion

Here we provide preliminary evidence that disease severity, lower limb weakness, cognitive impairment and executive dysfunction significantly influence mobility and balance in people with HD. Moreover, we show that key clinical features, when considered together, better explain performance on balance and mobility tasks than any single measure. Findings while preliminary, provide insight into the multiple clinical features that contribute to balance and mobility problems in HD, and provide a venue for targeted multidisciplinary rehabilitation strategies.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.baga.2014.04.002.

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