Chapter 6

Better global and cognitive functioning in choreatic versus hypokinetic-rigid Huntington's disease

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Abstract

Understanding the relation between predominantly choreatic and hypokinetic-rigid motor subtypes and cognitive and general functioning may contribute to knowledge about different motor-phenotypes in Huntington's disease. In the European Huntington's Disease Network Registry study, 1882 subjects were classified as being predominantly choreatic (N=528) or hypokinetic-rigid (N=432), according to their score on items of the total motor score a priori labelled as choreatic or hypokinetic-rigid; the other 922 patients were of a mixed type. The relationship between motor type and cognitive (verbal fluency, symbol digit modalities, Stroop colour, word and interference tests) and functional (total functional capacity) capacity was investigated using multiple linear regression. Motor subtype contributed significantly to the total functional capacity score (partial r^2: 7.8%; $p<0.001$) and to the five cognitive scores (partial r^2 values ranging from 2.0-8.4%; all p-values <0.001), patients with a predominantly choreatic motor phenotype performing better in all areas than patients with a hypokinetic-rigid motor phenotype.

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative disorder, caused by an unstable expansion of a CAG trinucleotide repeat on chromosome 4[1]. Although motor disturbances often stand out, the clinical presentation is also determined by behavioural problems and dementia[2].
HD is generally categorized as a hyperkinetic disorder[3]. Hypokinesia, however, also plays an important role in the motor presentation[4 5]. Clinically, three motor subtypes can be distinguished: choreatic, hypokinetic-rigid and mixed-motor type. It has been reported that the predominantly rigid type, typically seen in juvenile HD[6], is less common in adult-onset HD than chorea-predominant HD[7]. Nevertheless, some authors have stated that it is not chorea but hypokinesia-rigidity that is the core movement disorder in HD[8 9 10]. Most probably hyperkinesia and hypokinesia co-exist in HD, one of the two being predominant[10 11].

Because of the progressive nature of HD, motor symptoms worsen. Clinical observation suggests that this process is not uniform and that patients who present with predominantly choreatic or hypokinetic-rigid motor symptoms show different cognitive and functional profiles, a notion already stated by Brandt[12].
Several studies have investigated HD motor subtypes, but as the classification methods are heterogeneous, no uniform conclusions about the relation between motor type and clinical functioning can be drawn. Hyperkinesia in HD was found to be both related[13] and unrelated[9] to cognitive functioning, whereas hypokinesia was associated with cognitive[9 14] and functional impairment[4 5 8 15].

Investigating the cognitive and functional profiles of both motor types may add to the existing knowledge about motor functioning in HD patients, and may have implications for patient management.
We investigate the relationship between the predominant motor type and cognitive and general functioning and hypothesize that patients with predominantly choreatic motor characteristics function better than hypokinetic-rigid patients on both cognitive and general levels. We also examine the use of neuroleptics in both groups[16 17], and assess whether the motor phenotype is associated with disease duration.

METHODS

We used on-site, monitored data from the first visit of subjects with a CAG of $\geq$36 and a Unified Huntington's Disease Rating Scale (UHDRS)[18] total motor score (TMS) of $>$5, as recorded in the European Huntington's Disease Network Registry study. The number of subjects fulfilling these criteria was 1882. Variables consisted of the motor, function and cognitive parts of the UHDRS, CAG repeat

length, date-of-birth, gender, medication and educational level.
To enable classification into predominantly choreatic or hypokinetic-rigid motor phenotypes, certain TMS items were selected: for the choreatic subtype the items of the chorea scale, adding up to 28. For hypokinetic-rigidity finger taps, pronate-supinate hands, bradykinesia, rigidity, items measuring speed of movement and rigidity, again with a maximum of 28.
For subjects to be subdivided into predominantly choreatic or hypokinetic-rigid types, the total scores for the two subtypes had to differ by at least one standard deviation (i.e. 4 points). If the difference was smaller, it was considered to be a mixed motor type. This resulted in 528 choreatic, 432 hypokinetic-rigid and 922 mixed subjects. As we were interested in differences between predominantly choreatic and hypokinetic-rigid motor types, the mixed group was not included in analyses. The use of neuroleptic medication was scored as '1 = present' or '0 = absent'.

SPSS 17.0 was used for data analysis, and independent sample t-tests for group differences on demographic variables were performed, except for gender and neuroleptics (χ^2-test) and total functional capacity (Mann-Whitney U-test). Multiple linear regression models were constructed to evaluate the contribution of motor type to either cognition (verbal fluency, symbol digit modalities (SDMT) and Stroop colour, word and interference tests) or global functioning (total functional capacity; TFC). Age, gender, CAG repeat length, disease duration, TMS, and education were used as covariates and entered in one block. Motor type was entered as a binary variable. Partial correlation coefficients were calculated to examine the contribution of the separate covariates. To investigate whether the distribution of motor types was constant overt the disease course, disease duration was divided into quartiles and the distribution was examined with a χ^2-test. Statistical significance was set at $p<0.05$. For regression analysis the p-value was divided by six to correct for multiple testing, resulting in $p<0.008$.

RESULTS

Demographic analysis showed that the choreatic group was older, more often male, had been educated for longer ($p<0.005$), had a higher age at disease onset, shorter disease duration and lower CAG repeat (all p-values <0.001) compared to the hypokinetic-rigid group (Table 1). The choreatic group had a higher TFC and lower TMS ($p<0.001$). In all cognitive tests, hypokinetic-rigid subjects had lower scores than choreatic subjects ($p<0.001$). There was no difference between groups with regard to the number of participants using neuroleptic drugs.

Table 1: Demographics of whole group and of separate motor groups

	Whole group	Choreatic	Hypokinetic-rigid	P choreatic vs hypokinetic-rigid
N	1882	528	432	
Age (yrs)	50.6 (11.6)	52.2 (11.0)	49.8 (12.5)	<**0.005**
Gender f/m (%m)[a]	929/953 (51)	224/304 (58)	225/207 (48)	<**0.005**
Neuroleptics yes/no (%yes)[a]	1237/645 (66)	344/184 (65)	302/130 (70)	0.067
Years of education	11.2 (3.6)	11.4 (3.8)	10.8 (3.3)	<**0.005**
Age at disease onset (yrs)	43.6 (11.0)	45.2 (10.6)	41.7 (11.3)	<**0.001**
Disease duration (yrs)	7.0 (5.0)	6.9 (4.7)	8.1 (5.7)	<**0.001**
CAG large	44.1 (3.3)	43.7 (3.0)	45.0 (3.5)	<**0.001**
Total Functional Capacity[b]	9.0 (5)	10.0 (5)	6.0 (7)	<**0.001**
Total Motor Score	34.5 (18.4)	34.0 (16.4)	41.7 (19.8)	<**0.001**
Verbal fluency total score	17.7 (11.5)	19.4 (11.5)	13.7 (11.1)	<**0.001**
SDMT total score	20.6 (12)	22.8 (11.2)	15.4 (11.7)	<**0.001**
Stroop color total score	40.8 (17.5)	44.4 (17.2)	33.0 (17.0)	<**0.001**
Stroop word total score	55.2 (22.7)	60.5 (22.2)	44.3 (21.9)	<**0.001**
Stroop interference total score	22.2 (12)	24.7 (12.0)	17.4 (11.5)	<**0.001**

Note. Data are mean (standard deviation), expect for [a] (total number) and for [b] (median and interquartile range). Analyses are independent samples t-test, except for a (χ^2 test) and b (Mann-Whitney U-test). SDMT = Symbol Digit Modalities Test.

Linear regression analyses on cognitive functioning, taking differences in age, sex, education, disease duration, CAG and TMS into account (Table 2b-e), revealed that motor subtype was a predictor of all cognitive tests (all $p<0.001$). Patients in the hypokinetic-rigid group had significantly worse scores on all tests than those in the choreatic group. As revealed by the squared partial correlation coefficients, motor subtype was the second most contributing variable after TMS in all models ($p<0.001$) except verbal fluency, where it was the third most contributing factor ($p<0.001$).

Table 2: a-d. Linear regression analyses on total functional and cognitive scores

	B	SE B	Partial r^2	P-value
2a. Total Functional Capacity Score				
Constant	19.00	2.23		<**0.001**
Age (yrs)	-0.03	0.01	.000	<**0.005**
Gender	0.29	0.16	.003	0.075
Education (yrs)	0.10	0.02	.018	<**0.001**
Disease duration (yrs)	-0.14	0.02	.062	<**0.001**
CAG	-0.09	0.04	.005	0.029
Total Motor Score	-0.10	0.01	.297	<**0.001**
Motor subtype	-1.50	0.17	.078	<**0.001**
2b. Total Verbal Fluency Score				
Constant	48.08	8.71		<**0.001**
Age (yrs)	-0.08	0.05	0.003	0.070
Gender	-1.05	0.63	0.003	0.094
Education (yrs)	0.65	0.09	0.055	<**0.001**
Disease duration (yrs)	-0.11	0.07	0.003	0.116
CAG	-0.40	0.16	0.007	0.010
Total Motor Score	-0.27	0.02	0.157	<**0.001**
Motor subtype	-2.87	0.65	0.020	<**0.001**
2c. Symbol Digit Modalities Score				
Constant	70.49	7.60		<**0.001**
Age (yrs)	-0.26	0.04	0.045	<**0.001**
Gender	-0.56	0.55	0.001	0.303
Education (yrs)	0.56	0.08	0.053	<**0.001**
Disease duration (yrs)	-0.13	0.06	0.005	0.032
CAG	-0.52	0.14	0.015	<**0.001**
Total Motor Score	-0.33	0.02	0.278	<**0.001**
Motor subtype	-4.67	0.57	0.059	<**0.001**
2d. Stroop Colour Test Score				
Constant	84.96	12.07		<**0.001**
Age (yrs)	-0.24	0.06	0.014	<**0.001**
Gender	-0.93	0.87	0.000	0.286
Education (yrs)	0.53	0.12	0.020	<**0.001**
Disease duration (yrs)	-0.12	0.10	0.002	0.196
CAG	-0.16	0.22	0.001	0.454
Total Motor Score	-0.52	0.03	0.267	<**0.001**
Motor subtype	-7.39	0.90	0.066	<**0.001**

Table continues on next page.

Table 2: **(Continued)** e-f. Linear regression analyses on total functional and cognitive scores

	B	SE B	Partial r^2	P-value
2e. Stroop Word Test Score				
Constant	119.48	15.30		<**0.001**
Age (yrs)	-0.30	0.08	0.014	<**0.001**
Gender	-1.56	1.10	0.021	0.159
Education (yrs)	0.80	0.15	0.028	<**0.001**
Disease duration (yrs)	-0.37	0.12	0.096	<**0.005**
CAG	-0.35	0.27	0.002	0.206
Total Motor Score	-0.65	0.04	0.264	<**0.001**
Motor subtype	-10.62	1.14	0.084	<**0.001**
2f. Stroop Interference Test Score				
Constant	63.98	8.20		<**0.001**
Age (yrs)	-0.28	0.04	0.042	<**0.001**
Gender	-0.21	0.59	0.001	0.718
Education (yrs)	0.45	0.08	0.031	<**0.001**
Disease duration (yrs)	-0.13	0.07	0.004	0.043
CAG	-0.30	0.15	0.000	0.038
Total Motor Score	-0.32	0.02	0.229	<**0.001**
Motor subtype	-4.73	0.61	0.059	<**0.001**

Note. B=regression coefficient, SE B=standard error of B, r^2=squared partial correlation coefficients.

Motor subtype also contributed significantly to general functioning (TFC) ($p<0.001$) when the covariates were taken into account (Table 2a), and was the second most contributing variable after the TMS (partial $r^2=.078$, $p<0.001$). Together, independent variables explained 56% of the variance in TFC ($p<0.001$). Hypokinetic-rigid subjects performed significantly worse on TFC than choreatic subjects.

A χ^2-test revealed significant differences in the distribution of choreatic and hypokinetic-rigid subjects across disease duration quartile groups ($p= 0.008$), and shifted from slightly more choreatic than hypokinetic-rigid in the first three quartiles (I and II: 59% versus 41%, III: 56% versus 44%) to slightly more hypokinetic-rigid than choreatic in the last quartile (45% versus 55%).

DISCUSSION

We investigated the differences in clinical and cognitive performance between predominantly choreatic and hypokinetic-rigid HD patients. We found motor subtype defined by either predominantly chorea or hypokinesia-rigidity characteristics to be an independent predictor of both cognitive and general functioning, with choreatic patients functioning significantly better.

Investigating function and cognition in relation to predominantly choreatic or hypokinetic-rigid HD has not previously been carried out in this way. Earlier studies did, however, find that higher hypokinesia-rigidity scores were related to poorer cognitive and general functioning[4,5,14]. The lack of relation between choreatic movements and cognitive and functional impairment found in previous studies[9,13,15] seems to be in line with our finding that chorea in HD is characterized by better performance in both areas.
Clinically different motor subtypes have also been identified in Parkinsons disease (PD): tremor-dominant subtype (characterized by mild disease progression), akinetic-rigid subtype (where cognitive impairment is more severe), and postural instability and gait difficulty subtype (associated with cognitive impairment and severe disease progression)[19,20]. Comparable to our results, the hypokinetic PD subtypes are associated with poorer functioning than the subtype related to more hyperkinetic features.

The distribution of motor types across disease duration quartiles revealed a shift from slightly more choreatic than hypokinetic-rigid subjects in the first three quartiles to slightly more hypokinetic-rigid than choreatic subjects in the last quartile. Although these findings are based on group comparisons and do not necessarily reflect the probability that an individual patient follows the same course (i.e. the distribution across motor types of patients in the highest quartile of disease duration may already have been present in these same patients earlier in the disease), the alternative explanation that it does reflect the increasing probability that a patient converts from a more choreatic to a more hypokinetic-rigid motor type as disease duration lengthens is very well possible. This would support earlier findings on motor phenotype progression[7,21]. However, even if patients have an increased probability to convert to a more hypokinetic-rigid motor type with advancing disease, it does not account for our findings that the choreatic motor type is associated with better global and cognitive functioning because differences in disease duration were taken into account in the regression analyses. Furthermore, the differences in profiles can also not be explained by the influence of neuroleptic medication, as its use was comparable between groups.

Conclusions about our findings should be drawn with caution. The Registry database, due to its international nature, does not provide sufficient nor uniform

information about the dosages or indications for use of neuroleptics. Although neuroleptic use did not differ between groups, we cannot exclude the possibility that choreatic subjects are falsely assigned to the hypokinetic-rigid group due to medication-induced hypokinesia. Also, longitudinal analyses are essential to investigate the progression of choreatic and hypokinetic-rigid motor symptoms during the course of the disease. Replication of our results and further in-depth study of medication usage and degree of motor impairment is needed to ensure that the functional differences found can reliably be ascribed to different motor profiles.

To summarise, in a large cohort of patients with Huntington's disease, we found that predominantly choreatic HD is characterized by better global and cognitive functioning than hypokinetic-rigid HD, differences that could not be explained by differences in age or disease duration. Further research is, however, necessary.

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Competing interest

None.

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