Premanifest Huntington's disease : a study of early biomarkers

Jurgens, C.K.

Decreased performances on psychomotor tasks in HD premanifest carriers are due to subtle changes in both motor and cognitive functioning

Authors: C.K. Jurgens, MSc[1,3,4]; M.N.W. Witjes-Ané, MSc[1,4]; H.A.M. Middelkoop, PhD[1,2]; R.A.C. Roos, MD, PhD[1]

Institutional affiliations: From the [1]Department of Neurology of the Leiden University Medical Centre and the [2]Neuropsychology Unit of the Department of Psychology, Leiden University, Leiden. From the [3]Department of Psychology and the [4]Department of Geriatrics, Bronovo Hospital, The Hague, The Netherlands.

Submitted

Abstract

Objective: We studied the relations between motor impairment, cognitive deficits and mood and behavioural changes in 34 Huntington's Disease (HD) patients, 46 premanifest carriers and 88 non-carriers. Our main aim was to investigate whether relations found in patients were already present in premanifest carriers.

Methods: All participants were assessed using the Unified Huntington's Disease Rating Scale (UHDRS) and a neuropsychological battery that addressed global cognitive function, memory function and executive function, specifically psychomotor speed and cognitive flexibility.

Results: In patients, voluntary movement disturbances, global cognitive impairment and psychomotor decline were associated with functional decline. In carriers more behavioural complaints correlated with functional decline. Disease duration was only related to chorea. 'Pure' cognitive performance and motor functioning were not directly related, but were equally correlated with psychomotor speed in patients and in carriers. A dichotomy seemed, however, to occur: timed automatic tasks (like the Trailmaking Test part A) were more strongly related to motor deficits in patients while timed cognitive demanding tasks (like the Trailmaking Test part B) seemed to be more vulnerable to specific motor slowing in carriers.

Conclusions: The results corroborate other findings in that deficits in psychomotor speed are a key feature in (early) HD. A parallel evolution and progression of specific motor disturbances occur with specific cognitive deficits, whereas behavioural changes seem to be more variable.

Introduction

Huntington's disease (HD) is a neurodegenerative disorder with an autosomal dominant mode of inheritance, characterised by choreatic movements and disturbed voluntary movements, changes in mood and behaviour and cognitive decline.[1] These symptoms differ in time of onset and severity. Although the clinical diagnosis of HD is still based on the first motor symptoms, a positive family history, and confirmation by DNA-testing, changes in cognition and personality can precede motor changes.[2-4] Since the availability of predictive testing,[5] it is currently possible to investigate more closely how the disease develops, and consequently progresses, in premanifest carriers (i.e. without overt clinical signs) of the HD gene mutation (further labelled as carriers). However, the sequence of appearance of the first signs and the factors that influence the onset and the progression of the disease are still unclear.[6] Although CAG repeat length is associated with earlier disease onset,[7,8] few studies have reported an association between CAG repeat length and the progression of motor and cognitive deficits.[9,10] Inconsistent findings are reported about the associations between the disease duration and clinical and functional aspects of HD.[1] However, activities of daily living as measured by the Total Functional Capacity scale (TFC)[11,12] were reported to be associated with cognitive functioning,[13-15] motor functioning,[14,16,17] and behavioural functioning.[18] TFC was more influenced by voluntary movement than by chorea, suggesting that disorders in voluntary movements may be better indicators of functional disability and the evaluation of the stage and progression of HD.[19]
A linear relation between motor and cognitive functioning has been reported in patients,[11,17,20] although not consistently.[21] Some authors found that the cognitive disorder parallels the bradykinesia rather than the hyperkinesia.[22-24] With respect to psychiatric symptoms no associations with motor or cognitive functioning have been found, suggesting that these seem to occur more independently.[20,25]
Because of inconsistencies reported in carriers with regard to the occurrence of subtle changes (overview in Witjes-Ané et al[26]), research into the relations between HD characteristics in this group might enhance our insight into the development of HD. To our knowledge no study to date has attempted to specifically examine these relations in this particular group. In a previous study we found marginal changes in carriers on specific memory and psychomotor tasks.[26] Because of the known heterogeneity in cohorts with premanifest carriers, the aim was to investigate whether any relations found between motor, cognitive and behavioural aspects in the premanifest group matched those found in patients. Furthermore, we had a special interest in the extent to which motor and cognitive functioning contribute to performances in psychomotor tasks in the two groups.

Methods

Participants

Thirty-four patients with clinically diagnosed HD, 46 carriers without diagnosis and 88 non-carriers were included. The patients were followed in the European longitudinal study Core Assessment Protocol for Intracerebral Transplantation in Huntington's Disease (CAPIT-HD).[27] They were clinically diagnosed by a neurologist at the Department of Neurology, Leiden University Medical Center (LUMC) and referred by him for neuropsychological evaluation. The diagnosis was based on the

presence of motor signs, along with a positive family history, and was confirmed by DNA-testing in 28 patients. The age at onset of the disease was defined as the age when the first motor signs appeared.
Carriers and non-carriers described in this study participated in a longitudinal single-blind study to investigate the first clinical manifestations of HD. They had undergone predictive testing at the Department of Clinical Genetics. A repeat length ≥36 was considered confirmatory for carrying the HD gene. More details about participant recruitment and baseline protocol are described in the article by Witjes-Ané et al.[26] The protocols were approved by the Medical Ethics Committee from the LUMC and all participants gave their informed consent prior to their inclusion in the study.

Measures

UHDRS

All participants were assessed using the Unified Huntington's Disease Rating Scale (UHDRS)[11] which assesses four domains of functioning: motor performance, cognitive performance, behavioural abnormalities, and functional capacity. The motor assessment was performed blindly by a neurologist in case of carriers and non-carriers. Complaints about mood and behavioural changes were assessed using the behavioural part of the UHDRS by a psychologist. Functional status was rated according to the Total Functional Capacity score (TFC), which ranges from 0 (severely impaired) to 13 (normal) and assesses a person's capacity in relevant functional domains.

Neuropsychological Assessment

Patients were evaluated using the CAPIT-HD Neuropsychological Assessment Battery[27] which consisted of tests covering general intelligence, verbal memory, attention, and executive/ psychomotor function. The tests were selected to give a reasonably broad evaluation of cognitive functioning and to avoid floor and ceiling effects. Furthermore, they were chosen for their sensitivity to disease evolution and progression. Other tests, which were used at our department prior to the implementation of the CAPIT-HD protocol, were also applied for clinical and research purposes (arithmetic, spelling, visuo-constructive tasks).
Carriers and non-carriers were evaluated using a broad neuropsychological assessment of tests based on the CAPIT-HD protocol covering the same domains.[26] For the purpose of the present study we selected the tests shared by both protocols. We focused on executive tasks with a psychomotor component (further referred to as psychomotor tasks) which revealed decline early on in the disease or which were suitable for differentiating between carriers and non-carriers:[26,28] Trailmaking tests A and B (TMT), Stroop interference and Symbol Digit Modalities test (SDMT). Tasks that reflected more 'pure' global cognitive functioning were limited to WAIS-R Digit span, Mini Mental State Examination (MMSE), Wechsler Memory Scale (WMS) Memory Quotient (MQ) and verbal fluency (letters 'F' 'A' 'S'). The latter task was included in this domain because it proved to be significantly correlated (p= .000) with the WAIS-R total IQ (r= .41), verbal IQ (r= .45) and with the WMS MQ (r= .40) in the 88 non-carriers from this study but not with the above-mentioned psychomotor tasks (unpublished data). Word generation tasks are also known as measures of 'semantic memory'.[1]

Statistics

Behaviour and mood complaints were reflected by the Total Behavioural Score (TBS) obtained by adding the products of the frequency and severity for each item from the behavioural assessment of the UHDRS (mood/sadness, low self-esteem or guilt, anxiety, suicidal thoughts, disruptive or aggressive behaviour, irritable behaviour, obsessions, compulsions, delusions, and hallucinations).[29]
Analysis of motor functioning was restricted to the Total Motor Score (TMS) and to the subscales eye movement, voluntary movement and chorea, based on the literature and on clinical grounds.[1,23,30]
Statistical analysis was carried out using SPSS 16.0 for Windows package for computerised statistical analysis. Group characteristics and clinical differences were evaluated using χ^2 -tests for categorical data, Kruskal-Wallis tests for ordinal data, and analysis of variance (ANOVA's) for numerical data.
Post hoc comparisons were made with Bonferroni tests. Pearson correlation analyses were used to investigate relationships between the several clinical aspects in each group. TFC, disease duration, onset age and CAG-repeat length were also included in the investigation of patients.
The level of significance was set at p< .001. A more liberal p-level (less than .01) is also reported and considered to be marginally significant.

Results

Sociodemographic characteristics, the CAG repeat number and the functional status of the three groups are presented in *table 1*. A marginal difference in age was found between the groups. Post-hoc comparisons (Bonferroni) revealed that carriers were younger than patients (p= .004). The CAG-repeat length was higher in patients than in carriers (p= .004). Patients had a significantly lower score on the TFC compared to carriers and non-carriers. The mean age at onset in patients was 42 years (range: 20-63). The mean disease duration in patients was 4.7 years (range: 0.6-14).

Table 1. Characteristics and DNA-test results of 168 participants

Descriptives	HD Patients (n=34)	Carriers (n=46)	Non-carriers (n=88)	P
Gender M/F	18/16	16/30	40/48	.25[1]
Age at NPA, years (±SD)	47.0 (±10.2)	38.4 (±10.8)	41.7 (±11.4)	.005[2]
Education,				.08[3]
Less than High school	9 (27%)	4 (9%)	6 (7%)	
High school	18 (53%)	29 (63%)	56 (64%)	
More than high school/ University	7 (21%)	13 (28%)	26 (30%)	
Number of CAG-repeats, median (range)	46 (42-65)	43 (39-51)	19 (14-34)	.000[2]
TFC*	9.2 (±2.7)	12.8 (±0.6)	12.9 (±0.4)	.000[2]

[1]Chi-square test between all groups; [2]Anova; [3] Kruskal-Wallis test. *Lower scores correspond with worse functional capacity. HD: Huntington's Disease; NPA: neuropsychological assessment; TFC: Total Functional Capacity.

Group differences

Table 2 represents the results of the clinical assessment in the three groups. Analysis of variance revealed a significant difference in the total behavioural score between the groups (p< .001). Post hoc comparisons (Bonferroni) revealed that patients had more behavioural complaints than non-carriers. Furthermore, patients performed significantly worse than carriers and non-carriers on all motor items (p< .001) and neuropsychological tests (p< .001). The average scores in carriers were almost invariably slightly poorer than in non-carriers. This was, however, not significant.

Table 2. Clinical assessment in Huntingon's Disease patients, carriers and non-carriers

Clinical assessment	HD patients (n=34)	Carriers (n=46)	Non-carriers (n=88)
Behavioural assessment UHDRS, mean (±SD)[1]			
Total Behavioural Score (TBS)	18.61 (±19.41)	11.09 (±17.83)	5.51 (±9.73)
Motor assessment UHDRS, mean (±SD)[1]			
Total Motor Score (TMS) (0-124)[2]	31.42 (±21.52)	9.69 (±9.25)	6.50 (±7.22)
Total eye movement (0-24)[2]	7.45 (±5.46)	2.93 (±3.80)	2.23 (±3.31)
Total voluntary movement (0-32)[2]	8.77 (±6.50)	3.12 (±2.74)	2.07 (±2.65)
Total chorea (0-28)[2]	9.23 (±6.89)	1.71 (±3.01)	0.78 (±1.93)
Neuropsychological assessment, mean (±SD)			
WAIS-R, Digit span	6.06 (±2.55)	8.02 (±2.69)	8.55 (±2.18)
WMS, Memory Quotient[3]	89.88 (±19.45)	112.11 (±16.67)	119.67 (±13.37)
MMSE	25.00 (±3.48)	28.13 (±1.47)	28.56 (±1.22)
Verbal fluency (FAS)	18.15 (±12.25)	31.28 (±10.49)	32.86 (±10.64)
Trail Making Test A, in sec.[1]	76.97 (±60.58)	41.80 (±18.16)	32.51 (±10.35)
Trail Making Test B, in sec.[1]	153.13 (±82.57)	69.41 (±34.21)	54.41 (±18.65)
Stroop color word test, interference	26.03 (±9.46)	40.65 (±11.17)	43.71 (±8.12)
Symbol Digit Modalities Test	26.00 (±12.71)	46.56 (±11.98)	51.77 (±9.41)

[1]Lower scores correspond with better performance; [2]Range; [3]Patients: n= 16. HD: Huntington's Disease; UHDRS: Unified Huntington's Disease Rating Scale; WAIS-R: Wechsler Adult Intelligence Scale; WMS: Wechsler Memory Scale; MMSE: Mini Mental State Examination.

Correlations with TFC, disease duration and CAG repeat length in patients

Higher CAG repeat length only correlated significantly with younger onset age (r= -.74, p< .001). Relationships between clinical aspects and TFC, disease duration and CAG repeat length are presented in *table 3*. TFC score correlated marginally with the TMS (p= .008) and significantly with total voluntary movements (p= .001). With regard to the cognitive and psychomotor tasks, TFC correlated significantly with the MMSE (p< .001) and marginally with TMT-B (p= .01) and SDMT (p= .005). More motor abnormalities and worse cognitive performances were associated with lower functional capacity. Longer disease duration was related to more motor abnormalities on the TMS (p= .004) and the total chorea score (p= .002).

Table 3. Correlations (Pearson's r) of functional capacity, disease duration and CAG repeat length with clinical aspects in 34 Huntington's Disease patients

	TBS	TMS	Tot-eye	Tot-vol	Tot-chor	DSP	MQ[1]	MMSE	FAS	TMT-A	TMT-B	Stroop	SDMT
TFC	-.20	**-.48***	-.42	**-.57****	-.36	.35	.42	**.64****	.40	-.37	**-.46***	.42	**.48***
Disease dur.	.13	**.52***	.41	.46	**.54***	-.20	.01	-.10	-.30	.34	.26	-.14	-.33
CAG	-.32	-.07	.02	-.04	-.09	-.18	-.55	-.14	-.05	-.09	.11	-.21	-.04

[1]Patients: n=16. *Correlation is significant at the .01 level; **correlation is significant at the .001 level TBS: Total Behavioural Score; TMS: Total Motor Score; Tot-eye: Total eye movement score; Tot-vol; Total voluntary movement score; Tot-chor; Total chorea score; Dsp: WAIS-R digit span, standard score; MQ: WMS Memory Quotient; MMSE: Mini Mental State Examination; FAS: Verbal Fluency; TFC: Total Functional Capacity; Disease dur.: disease duration; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B: Stroop; Stroop Color Word Test, interference; SDMT; Symbol Digit Modalities Test.

Correlations among clinical aspects in patients, carriers and non-carriers

Total Behavioural Score with other clinical aspects

More mood and behavioural complaints on the TBS were related to lower TFC in carriers (r= -.59, p<.001) and were neither related to cognitive functioning nor to motor functioning in all groups.

Motor with cognitive functioning

More eye movement abnormalities correlated significantly with lower MMSE score (p= .001) and marginally with worse scores on Digit Span (p= .01) and FAS (p= .003) in patients (*table 4*). In the carrier group a marginal correlation was found between voluntary movement abnormalities and lower FAS score (p= .008).

Psychomotor speed with motor functioning

With regard to the psychomotor tasks we observed the most correlations with motor scores in patients and carriers (*table 4*). In patients, TMT-A and SDMT, rather than TMT-B and Stroop, were significantly associated with all motor variables. In carriers TMT-B, Stroop and SDMT were significantly correlated with most motor components. Non-carriers also showed a correlation pattern in motor functioning with the Stroop and SDMT. More motor abnormalities were related to worse scores on psychomotor tasks.

Psychomotor speed with cognitive functioning

Significant correlations between nearly all psychomotor tasks and the 'purely cognitive based' tasks, MMSE and FAS, were found in patients as well as in carriers (*table 5*). Furthermore all psychomotor tasks were associated with Digit Span in patients and with MQ in carriers. Worse cognitive scores were related to worse scores on psychomotor tasks.

Table 4. Correlations (Pearson's r) between behavioural, motor and cognitive functioning in 34 Huntington's Disease patients, 46 carriers and 88 non-carriers

	TBS			TMS			Tot-eye			Tot-vol			Tot-chor		
	P	C	N	P	C	N	P	C	N	P	C	N	P	C	N
Dsp	-.03	.02	.02	-.39	-.31	-.10	**-.46***	-.32	-.09	-.34	-.32	-.11	-.36	-.16	.03
MQ[1]	-.08	-.05	-.03	-.42	-.22	.05	-.50	-.20	.12	-.44	-.22	.03	-.32	-.11	-.01
MMSE	-.08	.05	.14	-.44	-.34	-.16	**-.58****	-.37	-.13	-.37	-.16	-.26	-.33	-.27	-.07
FAS	.00	-.06	-.18	**-.47***	-.36	-.10	**-.52***	-.21	-.09	-.39	**-.41***	-.01	-.45	-.26	-.18
TMT-A	-.07	-.10	-.08	**.66****	**.43***	.17	**.62****	.36	.17	**.55***	.35	.14	**.68****	.30	.11
TMT-B	.02	-.02	-.13	**.54***	**.55****	.25	**.51***	**.44***	.19	.42	**.48****	.26	**.55***	.38	.08
Stroop	.20	-.14	.10	**-.47***	**-.64****	**-.31***	**-.48***	**-.60****	**-.33***	-.40	**-.52****	**-.33***	-.45	**-.45****	-.05
SDMT	.05	-.14	.04	**-.71****	**-.49****	**-.42****	**-.76****	**-.41***	**-.40****	**-.60****	**-.47***	**-.41****	**-.63****	-.32	-.21

[1] Patients: n=16. *Correlation is significant at the .01 level; **correlation is significant at the .001 level; P: patients; C: carriers; N: non-carriers; Dsp: WAIS-R digit span, standard score; MQ: WMS Memory Quotient; MMSE: Mini Mental State Examination; FAS: Verbal Fluency; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B: Stroop: Stroop Color Word Test, interference; SDMT: Symbol Digit Modalities Test; TBS: Total Behavioural Score; TMS: Total Motor Score; Tot-eye: Total eye movement score; Tot-vol: Total voluntary movement score; Tot-chor: Total chorea score.

Table 5. Correlations (Pearson's r) between psychomotor tests and 'cognitive' based tests in 34 Huntington's Disease patients, 46 carriers and 88 non-carriers

	DSP			MQ[1]			MMSE			FAS		
	P	C	N	P	C	N	P	C	N	P	C	N
TMT-A	**-.48***	-.19	-.13	-.41	**-.52****	.12	**-.53***	**-.46****	-.02	**-.52***	**-.54****	-.12
TMT-B	**-.66****	-.33	**-.34****	-.51	**-.55****	-.07	**-.77****	**-.54****	-.01	**-.69****	**-.57****	-.04
Stroop	**.51***	**.57****	.19	.31	**.40***	.17	**.54****	**.39***	.05	**.53****	**.47****	.20
SDMT	**.72****	.32	**.33***	.57	**.50****	.15	**.72****	.30	.12	**.75****	**.65****	.21

[1] Patients: n=16. *Correlation is significant at the .01 level; **correlation is significant at the .001 level; P: patients; C: carriers; N: non-carriers; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B: Stroop: Stroop Color Word Test, interference; SDMT: Symbol Digit Modalities Test; Dsp: WAIS-R digit span, standard score; MQ: WMS Memory Quotient; MMSE: Mini Mental State Examination; FAS: Verbal Fluency.

Discussion

The purpose of the present study was to investigate whether the patterns of relations between motor, cognitive and behavioural changes found in HD patients were already present in carriers.

Clinical aspects in patients. The findings of the present study largely corroborate other reports about HD patients, showing worse performances compared to carriers and non-carriers;[1] impairment in activities of daily living (ADL), measured here with the TFC[12], correlated with the more hypokinetic feature of HD rather than with chorea,[24,31] suggesting that this sign would be a more appropriate criterion than hyperkinesia for the evolution of disease stages;[23,30] impaired TFC was also found to be related with cognitive decline (MMSE)[18,32] and with psychomotor slowing.[13,14,32,33] Functional capacity seems to be more reliable than disease duration to monitor the progression of HD, since there is a lack of correlation between disease duration and HD signs, except for chorea.

Mood and behaviour. Comparable to most studies, mood and behavioural symptoms were not related to either motor or cognitive functioning.[11,20,25,34] This lack of correlation confirms that behavioural aspects are more independent in progression than cognitive and motor symptoms, also illustrated by the finding in our study that patients did not differ significantly from carriers as far as mood and behaviour were concerned. Impairment in ADL was not associated with a larger number of mood and behavioural symptoms in patients. The carrier group, however, showed a strong relationship between the behavioural assessment and functional capacity, suggesting that complaints about mood and behaviour seem to influence daily functioning in some carriers, resulting, for example, in a reduced capacity for accustomed work. Functional decline was reported to be influenced by apathy/executive dysfunction in patients, even after controlling for motor and cognitive deficits.[35] Amongst the behavioural problems occurring in HD, the progression of apathy differs from the progression of depression and irritability and is, like the disturbance in voluntary movement, related to cognitive deficits.[34,36] The 'lack' of 'initiative' as well as the 'lack' of 'movement' must not be underestimated in research with carriers. Although apathy was not assessed in the present study the marginal correlation found between verbal fluency and voluntary movements might indicate an initiative problem in some carriers.

Associations between motor and cognitive functioning. The correlation patterns in carriers were similar to those seen in patients: no direct association was found between motor and 'pure' cognitive functioning, however these domains correlated equally with psychomotor tasks. Note that associations with the SDMT and the Stroop were less specific to HD as they also occurred in non-carriers.

A relatively parallel decline in motor and cognitive function, rather than a causal one, has been suggested.[20,23] These characteristics would progress side by side, but not at the same speed. Motor impairment has been associated with some WAIS verbal and performance scores, with memory and perceptual/attentional aspects.[17,20,23] In accordance with our findings, however, it was found to be related more strongly to tasks that have high demands on motor speed rather than accuracy.[22,24,34] Psychomotor task performances were related to eye movement disturbances as well as attention deficits (Digit Span), only in the patients from the present study. Psychological, functional anatomical and neurological research has shown that attentional processes are closely linked to oculomotor processes.[37] The eye movements component was related to all 'pure' cognitive tasks, except for the MQ. This was probably due to different statistical power because of the smaller number of patients evaluated with the WMS, as the correlation coefficient is similar to the others. Impairment of specific

motor functions (i.e. eye movement disturbances) might change linearly with the global cognitive deficits. In previous studies voluntary movement disturbances, rather than severity of chorea was found to be related with cognitive deficits.[17,22-24] Tasks examining voluntary movement disturbances require programming and execution of sequential motor acts.[17] Impairment in sequencing operations is common in HD patients[22,38] and also present in premanifest carriers.[39-41] The present findings showed that stronger relations occurred in patients between motor functioning and performance on the TMT part A rather than on part B. Inversely, TMT part B was related more strongly to global cognitive functioning than part A. This suggests a stronger influence of motor decline in automatic tasks in patients. In carriers, however, the TMT-A would be influenced by cognitive impairment rather than by motor deficits (probably due to a subset of carriers who showed cognitive impairment[26]), while eye and voluntary movements disturbances would begin to play a role in TMT-B performance, i.e. when the task becomes more cognitive demanding. These motor characteristics were reported to be early signs of HD.[1,30] Timed cognitively demanding tests would be more vulnerable to motor slowing in carriers than timed automatic tests.

Concluding remarks. The present study showed that correlation patterns found in HD carriers were more pronounced than in non-carriers. More interestingly, they resembled those seen in patients with regard to the equal contribution of cognitive and motor aspects to psychomotor speed. These findings extend the results of our previous research[26] and are in accordance with other studies which reported that psychomotor slowing is a key characteristic in (early) HD.[2,41,42] A subset of carriers would already show some cognitive or motor deficits, or both, reflected in the correlation patterns found with regard to psychomotor tasks.

The relevance of including distinct components (instead of global cognitive, motor or behavioural scores) when examining the evolution and progression of HD characteristics is clear from the present findings. Although the patterns were similar in carriers and patients, some differences occurred especially in the interpretation of timed automatic based tasks and timed cognitively demanding tasks. Furthermore concomitant progression of motor and 'pure' cognitive functioning in patients was seen for eye movement disturbances, rather than voluntary movements and chorea, suggesting a non-linear progression in distinct motor aspects. Also, when reporting about cognitive deficits in relation to motor impairment, psychomotor slowing has to be differentiated from other cognitive aspects like intelligence, memory or 'executive' deficits. The present study did not take into account the various stages in the patient group because the number of patients was too small. More specific relations would probably be found, as progression in motor and cognitive deficits may differ at each stage.[13,32] Additional longitudinal research is needed to extend these cross-sectional findings in carriers, also including quantitative motor assessment being a valuable measure of motor impairment.

Acknowledgements

The authors thank J.P.P. van Vugt for performing most motor assessments. Financial support was provided by the Netherlands Organisation for Scientific Research (NWO), Grant 970-10-021.

References

1. Bates G, Harper PS, Jones L. Huntington's disease. Oxford University Press, 2002.
2. Solomon AC, Stout JC, Weaver M et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord. 2008; 23:1830-6.
3. Squitieri F, Cannella M, Giallonardo P et al. Onset and pre-onset studies to define the Huntington's disease natural history. Brain Res.Bull. 2001; 56:233-8.
4. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J.Neuropsychiatry Clin.Neurosci. 2007;19:441-8.
5. Huntington's Disease Collaborative Research Group. A Novel Gene Containing A Trinucleotide Repeat That Is Expanded and Unstable on Huntingtons-Disease Chromosomes. Cell 1993; 72:971-83.
6. Georgiou-Karistianis N, Smith E, Bradshaw JL et al. Future directions in research with presymptomatic individuals carrying the gene for Huntington's disease. Brain Res.Bull. 2003; 59:331-8.
7. Duyao M, Ambrose C, Myers R et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat.Genet. 1993; 4:387-92.
8. Djousse L, Knowlton B, Hayden M et al. Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. Am.J.Med.Genet.A 2003; 119A:279-82.
9. Brandt J, Bylsma FW, Gross R et al. Trinucleotide repeat length and clinical progression in Huntington's disease. Neurology 1996; 46:527-31.
10. Rosenblatt A, Liang KY, Zhou H et al. The association of CAG repeat length with clinical progression in Huntington disease. Neurology 2006; 66:1016-20.
11. Huntington Study Group. Unified Huntington's disease rating scale: Reliability and consistency. Movement Disorders 1996; 11:136-42.
12. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979; 29:1-3.
13. Marder K, Zhao H, Myers RH et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology 2000; 54:452-8.
14. Rothlind JC, Bylsma FW, Peyser C et al. Cognitive and motor correlates of everyday functioning in early Huntington's disease. J.Nerv.Ment.Dis. 1993; 181:194-9.
15. Bamford KA, Caine ED, Kido DK et al. A Prospective Evaluation of Cognitive Decline in Early Huntingtons-Disease - Functional and Radiographic Correlates. Neurology 1995; 45:1867-73.
16. Nehl C, Paulsen JS. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. J.Nerv.Ment.Dis. 2004; 192:72-4.
17. Brandt J, Strauss ME, Larus J et al. Clinical correlates of dementia and disability in Huntington's disease. J.Clin.Neuropsychol. 1984; 6:401-12.
18. Mayeux R, Stern Y, Herman A et al. Correlates of early disability in Huntington's disease. Ann.Neurol. 1986; 20:727-31.
19. Girotti F, Carella F, Scigliano G et al. Effect of neuroleptic treatment on involuntary movements and motor performances in Huntington's disease. J.Neurol.Neurosurg.Psychiatry 1984; 47:848-52.
20. Zappacosta B, Monza D, Meoni C et al. Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. Arch.Neurol. 1996; 53:493-7.
21. Georgiou N, Bradshaw JL, Phillips JG et al. Reliance on advance information and movement

sequencing in Huntington's disease. Mov Disord. 1995; 10:472-81.
22. Snowden J, Craufurd D, Griffiths H et al. Longitudinal evaluation of cognitive disorder in Huntington's disease. Journal of the International Neuropsychological Society 2001; 7:33-44.
23. Girotti F, Marano R, Soliveri P et al. Relationship between motor and cognitive disorders in Huntington's disease. J.Neurol. 1988; 235:454-7.
24. Snowden JS, Craufurd D, Griffiths HL et al. Awareness of involuntary movements in Huntington disease. Arch.Neurol. 1998; 55:801-5.
25. Caine ED, Shoulson I. Psychiatric syndromes in Huntington's disease. Am.J.Psychiatry 1983; 140:728-33.
26. Witjes-Ané MNW, Vegter-van der Vlis M, van Vugt JPP et al. Cognitive and motor functioning in gene carriers for Huntington's disease: A baseline study. Journal of Neuropsychiatry and Clinical Neurosciences 2003; 15:7-16.
27. Quinn N, Brown R, Craufurd D et al. Core Assessment Program for Intracerebral Transplantation in Huntington's Disease (CAPIT-HD). Mov Disord. 1996; 11:143-50.
28. Zakzanis KK. The subcortical dementia of Huntington's disease. J.Clin.Exp.Neuropsychol. 1998; 20:565-78.
29. Witjes-Ané MNW, Zwinderman AH, Tibben A et al. Behavioural complaints in participants who underwent predictive testing for Huntington's disease. Journal of Medical Genetics 2002; 39:857-62.
30. Sanchez-Pernaute R, Kunig G, del Barrio AA et al. Bradykinesia in early Huntington's disease. Neurology 2000; 54:119-25.
31. Bylsma FW, Rothlind J, Hall MR et al. Assessment of adaptive functioning in Huntington's disease. Mov Disord. 1993; 8:183-90.
32. Gomez-Tortosa E, Del BA, Garcia Ruiz PJ et al. Severity of cognitive impairment in juvenile and late-onset Huntington disease. Arch.Neurol. 1998; 55:835-43.
33. Bamford KA, Caine ED, Kido DK et al. Clinical-pathologic correlation in Huntington's disease: a neuropsychological and computed tomography study. Neurology 1989; 39:796-801.
34. Thompson JC, Snowden JS, Craufurd D et al. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. J.Neuropsychiatry Clin.Neurosci. 2002; 14:37-43.
35. Hamilton JM, Salmon DP, Corey-Bloom J et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J.Neurol.Neurosurg.Psychiatry 2003; 74:120-2.
36. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol.Behav.Neurol. 2001; 14:219-26.
37. Corbetta M. Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? Proc.Natl.Acad.Sci.U.S.A 1998; 95:831-8.
38. Lawrence AD, Sahakian BJ, Hodges JR et al. Executive and mnemonic functions in early Huntington's disease. Brain 1996; 119 (Pt 5):1633-45.
39. Foroud T, Siemers E, Kleindorfer D et al. Cognitive scores in carriers of Huntington's disease gene compared to noncarriers. Ann.Neurol. 1995; 37:657-64.
40. Kirkwood SC, Siemers E, Hodes ME et al. Subtle changes among presymptomatic carriers of the Huntington's disease gene. J.Neurol.Neurosurg.Psychiatry 2000; 69:773-9.
41. Snowden JS, Craufurd D, Thompson J et al. Psychomotor, executive, and memory function in preclinical Huntington's disease. Journal of Clinical and Experimental Neuropsychology 2002; 24:133-45.

42. Bachoud-Levi AC, Maison P, Bartolomeo P et al. Retest effects and cognitive decline in longitudinal follow-up of patients with early HD. Neurology 2001; 56:1052-8.