Huntington's disease : hypothalamic, endocrine and metabolic aspects

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Chapter 5

Autonomic symptoms in patients and premanifest mutation carriers of Huntington's disease

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ABSTRACT

Objective: Although autonomic function tests have revealed abnormalities of the autonomic nervous system in Huntington's disease (HD), autonomic symptoms and their association with other symptoms and signs of HD have not yet been assessed in large groups of patients or premanifest mutation carriers. We therefore aimed to delineate the characteristics and correlates of autonomic symptoms in HD. *Subjects & methods:* Using the SCOPA-AUT and Beck Depression Inventory questionnaires, autonomic symptoms and depressed mood were assessed in 63 HD patients, 21 premanifest mutation carriers and 85 controls. The Unified Huntington's Disease Rating Scale was used to assess other HD symptoms and signs. *Results:* Relative to controls, HD patients experienced significantly more gastrointestinal, urinary, cardiovascular and, in men, sexual problems. The most prevalent symptoms were swallowing difficulties, erection and ejaculation problems, dysphagia, sialorrhea, early abdominal fullness, straining for defecation, fecal and urinary incontinence, urgency, incomplete bladder emptying, and light-headedness while standing. Premanifest mutation carriers experienced significantly more swallowing difficulties and light-headedness on standing up compared with controls. In HD patients, autonomic symptoms were associated with a greater degree of functional disability, more severe depression and antidepressant drugs use; however, depression was the only independent predictor of autonomic dysfunction. *Conclusions:* Autonomic symptoms are highly prevalent in HD patients and may even precede the onset of motor signs. Moreover, autonomic dysfunction is related to functional disability and depression in HD.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat sequence in the gene encoding the protein huntingtin.[1] The disease is characterized by motor impairment, cognitive deterioration, behavioral problems and progressive weight loss.[1,2] Although less well-known, autonomic nervous system (ANS) dysfunction can also accompany HD.[3] Indeed, standardized ANS tests, including the blood pressure response to sustained handgrip,[4,5] orthostatic blood pressure test,[4-7] sympathetic skin response,[4,6,7] the pupillary light reflex latency,[4] and heart rate variability assessment at rest and during various maneuvers,[4-8] have revealed abnormalities in both the sympathetic and parasympathetic branches of the ANS in HD.

Autonomic symptoms such as hyperhydrosis, micturition and swallowing difficulties,[9-11] sexual dysfunction,[12] as well as complaints suggestive of orthostatic intolerance[13,14] have been reported in small groups of HD patients. Moreover, although autonomic symptoms are thought to be most prominent in the advanced stages of the disease,[15,16] complaints of possible autonomic origin such as dizziness after standing up, excessive perspiration and tachycardia have also been described in mildly disabled HD patients and even in otherwise asymptomatic mutation carriers.[5] However, the extent of autonomic complaints as well as their association with other symptoms and signs of the disease have not yet been studied in large groups of HD patients or premanifest mutation carriers.

Therefore, the objectives of the present study were to (1) delineate the characteristics and frequency of autonomic symptoms in HD patients and premanifest mutation carriers in comparison with non-mutation carrying control subjects, and (2) to assess the relation between autonomic symptoms and various clinical characteristics in order to identify important predictors of autonomic problems in HD patients.

METHODS

Design and participants

HD patients and premanifest mutation carriers were successively recruited from the outpatient clinic of the department of Neurology of the Leiden University Medical Center (LUMC) between June 2007 and December 2008. Control subjects were recruited over the same period and were randomly selected non-mutation carrying family members, partners or acquaintances of participating patients, employees at our department or their acquaintances. Exclusion criteria for both groups were the diagnosis of a primary ANS disorder or a disease of the central nervous system unrelated to HD. All patients and premanifest mutation carriers were seen once or twice a year as part of their regular care. Three weeks before the scheduled annual appointments two identical postal surveys containing standardized questionnaires were sent to these subjects. The forms in one of the surveys were completed by the patients or premanifest mutation carriers themselves (or by the primary caregivers on their behalf) while, whenever possible, the other survey had to be completed by a non-mutation carrying family member, the partner or an acquaintance. The patients and premanifest mutation carriers brought their survey to the scheduled appointment and simultaneously provided contact data for the control subject. When questionnaires were not fully completed or were not received within one month, subjects were reminded

by phone. The study protocol was approved by the medical ethics committee of the LUMC and all participants gave written informed consent.

Measurement Instruments

The clinical diagnosis of HD was made by a neurologist specialized in movement disorders (R.A.C.R.). The clinical condition of HD patients was assessed according to the motor, cognitive, behavioral and functional subscales of the Unified Huntington Disease Rating Scale (UHDRS).[17] Premanifest status was defined as a score of <5 on the UHDRS motor scale. Symptoms of depression were evaluated by the Beck Depression Inventory (BDI).[18] Autonomic symptoms were assessed using the SCOPA-AUT questionnaire.[19] Although the SCOPA-AUT questionnaire was originally developed for patients with Parkinson's disease, the items cover a broad area of autonomic domains that may also be affected in HD.[3] The SCOPA-AUT questionnaire was selected as it is quick and easy to administer and has already been demonstrated to have a good test-retest reliability in a Dutch population (both Parkinson's disease patients and controls).[19,20] The SCOPA-AUT consists of 25 items assessing the following domains: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2 items for men and 2 items for women) dysfunction. The frequency of the problem was evaluated with four response options ranging from 0 ("never") to 3 ("often"). The urinary and sexual regions have an additional response option, to indicate whether a subject used a catheter or had not been sexually active.[19] In order to simplify comparison, the total and domain scores were all converted into relative scores with a range of 0 to 100, with higher scores indicating more severe impairment. In addition, to assess the relative frequency of each specific autonomic symptom in HD, the percentages within each participating group with item scores of ≥ 1 were compared.

Statistical Analysis

Mean differences between HD patients, premanifest mutation carriers, partners and other controls were assessed using χ^2-tests and one-way analysis of variance (ANOVA) after a square-root transformation in case of non-normal distribution. Tukey's test (in case of equal variances) or Dunnett's T3 test (in case of unequal variances) was used for post-hoc analysis. In HD patients, partial correlations were used to assess the relation of each clinical variable — such as various UHDRS subscores and medication use (differentiating between sleep medications, antidepressants, neuroleptics and a rest group) — with the total autonomic symptom score, while correcting for the effects of age and sex. To identify which predictor variables were independently associated with the total autonomic score in HD patients, we also used a forward stepwise regression procedure with entry and removal probabilities for F of 0.05 and 0.10, respectively. An independent predictor of autonomic dysfunction is a variable that remains significantly associated with autonomic symptom severity after adjustment for the effects of other significant predictor variables. Additionally, in HD patients, Spearman's correlation coefficient was used to assess the association between motor impairment and each domain score separately, as well as to assess the correlates of sexual dysfunction. All tests were two-tailed and values of $p < 0.05$ were considered significant. The analyses were performed with SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Participants

In total, 169 subjects participated in this study (Table 1). Of these 84 were mutation carriers (63 had manifest HD and 21 were premanifest), and 85 were non-mutation carrying subjects. As autonomic problems, such as sexual dysfunction, of the mutation carriers may affect their partners, non-mutation carriers were further divided into a partner group and a group consisting of other controls (Table 1). The four groups did not differ with respect to age, sex, and BMI (all $p > 0.453$). Mutation carriers were significantly more depressed compared with non-carriers ($p < 0.001$), but the degree of depression did not differ between manifest and premanifest HD subjects (p=0.10). HD patients used significantly more antidepressant and neuroleptic drugs than the other groups (Table 1).

Table 1. Characteristics of the study participants

	HD patients	Premanifest mutation carriers	Partners	Controls	*p*-value
No. of participants	63	21	21	64	-
Sex (% men)	29/34 (46.0)	9/12 (42.9)	10/11 (47.6)	27/37 (42.2)	0.959†
Age, mean (SD), yr	48.5 (10.7)	44.4 (8.7)	48.3 (9.1)	47.4 (10.4)	0.453‡
BMI, mean (SD)	25.3 (4.0)	25.5 (3.4)	25.5 (4.9)	25.3 (4.6)	0.997‡
BDI score, mean (SD)	11.8 (9.4)	8.1 (8.4)	4.3 (5.7)	4.6 (4.8)	<0.001‡
Sleep medication, n (%)	16 (25.4)	3 (14.3)	5 (23.8)	5 (7.8)	0.052†
Antidepressants, n (%)	23 (36.5)	1 (4.8)	4 (19.0)	1 (1.6)	<0.001†
Neuroleptics, n (%)	17 (27.0)	1 (4.8)	0	0	<0.001†
Other medication, n (%)	29 (46.0)	9 (42.9)	11 (52.4)	16 (25.0)	0.138†

†) χ^2-tests.

‡) One-way ANOVAs.

Legend: BDI = Beck's Depression Inventory; BMI = Body Mass Index; HD = Huntington's disease

Autonomic symptoms: domains

The SCOPA-AUT items regarding sexual function were answered with 'not applicable' by a substantial minority in all groups, therefore, these items were not included for the calculation of the total score. Overall, patients with HD reported significantly more autonomic symptoms compared with both partners and controls as indicated by a higher total SCOPA-AUT score (Table 2). However, the total SCOPA-AUT score did not differ between HD patients and premanifest mutation carriers (p=0.33). Compared with partners and controls, HD patients experienced significantly more gastrointestinal, cardiovascular and, in men, sexual problems. HD patients also reported significantly more gastrointestinal and male sexual problems than premanifest mutation carriers (Table 2). In general, the autonomic domain scores of premanifest mutation carriers were in between those of HD patients and non-mutation carriers.

Table 2. Autonomic symptoms severity (range 0 to 100) and frequency (% with an item score ≥ 1) in the study population.

	HD patients	Premanifest	Partners	Controls	*p*-value[1]
Total score (median, IQR)[2]	**16 (10-24)** [a,c]	**14 (7-18)**	**7 (4-12)**	**10 (6-14)**	**<0.001****
Gastrointestinal domain (median, IQR)[2]	**14 (5-19)** [a,b,c]	**5 (2-10)** [e]	**0 (0-5)**	**5 (0-10)**	**<0.001****
Swallowing/choking (%)	71[a,b,c]	48[d,e]	5[f]	16	<0.001**
Sialorrhea (%)	32[a,b,c]	0	0	11	<0.001**
Dysphagia (%)	35[a,c]	14	5	8	<0.001**
Early abdominal fullness (%)	32[a]	24	25	16	0.206
Constipation (%)	11	10	5	9	0.882
Straining for defecation (%)	37[c]	33	10	27	0.134
Fecal incontinence (%)	16[a]	5	0	3	0.021*
Urinary domain (median, IQR)[2]	**22 (11-39)**	**17 (11-22)**	**11 (7-17)**	**17 (11-26)**	**0.066***
Urgency (%)	44[a,b,c]	19	5	27	0.003**
Urinary incontinence (%)	32[a]	14	10	14	0.038*
Incomplete emptying (%)	27[c]	14	5	20	0.164
Weak stream of urine (%)	29	14	10	20	0.264
Frequency (%)	68	81	70	78	0.507
Nocturia (%)	78	81	70[f]	89	0.189
Cardiovascular domain (median, IQR)[2]	**0 (0-11)** [a]	**0 (0-11)**	**0 (0-8)**	**0 (0-0)**	**0.047***
Light-headed when standing up (%)	33[a]	38[d]	25	17	0.123
Light-headed when standing for some time (%)	16[a]	5	0	3	0.021*
Syncope in the past 6 months (%)	5	0	0	0	0.165
Thermoregulatory domain (median, IQR)[2]	**17 (0-25)**	**17 (0-29)**	**8 (0-25)**	**17 (0-25)**	**0.751**
Hyperhidrosis during the day (%)	37	43	30	42	0.742
Hyperhidrosis during the night (%)	41	52	45	48	0.784
Cold intolerance (%)	38	33	25	27	0.491
Heat intolerance (%)	44	38	35	33	0.590
Pupillomotor domain (median, IQR)[2]	**0 (0-0)**	**0 (0-33)**	**0 (0-33)**	**0 (0-33)**	**0.855**
Over-sensitive for bright light (%)	24	33	35	30	0.711
Sexual domain: men (median, IQR)[2]	**33 (0-58)** [a,b,c]	**0 (0-8)**	**0 (0-0)**	**0 (0-0)**	**0.004****
Erection problem (%)	67[a,b,c]	22	11	22	<0.001**
Ejaculation problem (%)	59[a,b,c]	0	11	19	<0.001**
'Not applicable' (%)	21	0	10	7	0.275
Sexual domain: women (median, IQR)[2]	**0 (0-17)**	**8 (0-42)**	**0 (0-17)**	**8 (0-29)**	**0.562**
Women: Vaginal lubrication (%)	53	42	55	49	0.904
Women: Problem with orgasm (%)	53	67	46	51	0.755
'Not applicable'	38	33	36	24	0.633

[1]) Differences in means were assessed by one-way analysis of variance (after a square-root transformation in case of non-normal distribution) with Tukey's test (in case of equal variances) or Dunnett's T3 test (in case of unequal variances) for post-hoc analysis. Differences in proportions were assessed by the χ^2-test. * $p<0.05$; ** $p<0.01$

[2]) To simplify comparison, the total and domain scores were all converted into relative scores with a range of 0 to100. IQR = interquartile range

[a]) Patients vs. controls ($p<0.05$)

[b]) Patients vs. premanifest mutation carriers ($p<0.05$)

[c]) Patients vs. partners ($p<0.05$)

[d]) Premanifest mutation carriers vs. control ($p<0.05$)

[e]) Premanifest mutation carriers vs. partners ($p<0.05$)

[f]) Partners vs. controls ($p<0.05$)

Autonomic symptoms: frequency

The largest differences between HD patients relative to controls existed for the frequency of swallowing/choking (71 vs. 16%), erection problems (67 vs. 22%), ejaculation problems (59 vs. 19%), dysphagia (35 vs. 8%), and sialorrhea (32 vs. 11%) (Table 2). Other relatively prevalent autonomic symptoms in HD patients were early abdominal fullness, straining for defecation, fecal and urinary incontinence, urgency, incomplete bladder emptying, and light-headedness while standing (up). Of these symptoms, only swallowing difficulties, sialorrhea, urgency, and erection and ejaculation problems were also more frequent in HD patients compared to premanifest mutation carriers. Premanifest mutation carriers experienced significantly more swallowing difficulties and light-headedness on standing up compared with controls (Table 2).

Predictors of autonomic dysfunction in HD patients

Only UHDRS functional indices, i.e. total functional capacity, functional assessment and independence score, were significantly associated with the total autonomic dysfunction score in HD patients (Table 3). The total score also positively correlated with depressive symptoms as well as use of antidepressant drugs (both $p<0.045$). Moreover, stepwise regression identified depressive symptoms as the only independent predictor of autonomic dysfunction, accounting for 32% of the variation (Table 3). Motor impairment was not significantly associated with any domain score in HD patients.(all $p \geq 0.171$).

Table 3. Correlates of autonomic dysunction in HD patients

	SCOPA-AUT total score	
	Correlation† **(r ; p-value)**	**Stepwise regression†** **(effect; SE)**
Motor score	-0.00 (0.975)	-
TFC	-0.37 (0.006) **	-
Functional assessment	-0.35 (0.008) **	-
Independence score	-0.28 (0.038) *	-
Cognitive score	-0.10 (0.574)	-
Behavior score	0.04 (0.796)	-
BDI	0.57 (<0.001) **	0.46 (0.18) **
BMI	0.22 (0.086)	-
Normal CAG repeat size	0.01 (0.923)	-
Mutant CAG repeat size	0.03 (0.833)	-
Sleeping medication	0.23 (0.081)	-
Antidepressants	0.26 (0.045) *	-
Neuroleptics	0.13 (0.303)	-
Rest	-0.04 (0.735)	-

†) All results are corrected for age and sex.
*) $p < 0.05$; ** $p < 0.01$.

Legend: BDI = Beck's Depression Inventory; BMI = Body Mass Index; HD = Huntington's disease; HD = Huntington's disease; SCOPA-AUT = Scales for outcomes in Parkinson's disease-autonomic symptoms; TFC = Total Functional Capacity

As the items regarding sexual function were gender specific and not included in the total SCOPA-AUT score, we assessed this domain separately. In male HD patients, sexual dysfunction was significantly associated with all UHDRS functional indices (r from -0.49 to -0.61, $p \leq 0.028$), BMI (r=+0.54, p=0.012), depressive symptoms (r=+0.52, p=0.017), and use of antidepressants (r=+0.54, p=0.013). In female HD patients, however, sexual dysfunction was only significantly related to the behavioural score (r = -0.48, 0.045).

DISCUSSION

To our knowledge, this is the largest cohort of HD patients and premanifest mutation carriers whose autonomic symptoms have been systematically assessed in relation to other clinical symptoms and signs. We found a range of autonomic symptoms in HD patients, particularly in the gastrointestinal, urinary, cardiovascular and male sexual domains, some of which were also present in premanifest mutation carriers. These findings indicate that, autonomic symptoms are highly prevalent in HD patients and may even precede the onset of motor signs. In addition, we found that a greater degree of autonomic dysfunction in HD patients was associated with more functional disability as well as more depressive symptoms.

The most prominent complaints in HD patients concerned the gastrointestinal tract and included swallowing difficulties, dysphagia and sialorrhea. These symptoms may partly be accounted for by skeletal muscle incoordination due to striatal pathology.[10] However, the absence of an association between gastrointestinal symptoms and UHDRS motor score, as well as the relatively high prevalence of swallowing difficulties even in premanifest mutation carriers suggest that ANS dysfunction is also likely to contribute to gastrointestinal problems in HD. This notion is further supported by the comparatively high prevalence of other symptoms in HD patients, including early abdominal fullness, straining for defecation, urgency, incomplete bladder emptying, and postural dizziness, which cannot be ascribed to motor impairment alone. Nevertheless, although our findings suggest that ANS dysfunction is likely to contribute to the various symptoms enlisted in Table 2, we cannot exclude other potential contributing factors such as endocrine and peripheral abnormalities.[3,21] Therefore, further studies simultaneously applying both subjective and objective measures, such as the composite autonomic scoring scale,[22] should be undertaken to more accurately delineate the role of ANS dysfunction in the pathogenesis of the aforementioned symptoms in HD.

Interestingly, while erection and ejaculation problems were very prominent in male HD patients, sexual dysfunction was not obvious in female patients. However, relatively more HD patients than controls, and relatively more females than males, answered ‘not applicable’ to one or both of the sexual items in the questionnaire, which could indicate sexual hypofunction.[12] Our results may therefore represent underestimates of the actual prevalence of sexual dysfunction in, particularly female, HD patients.

Autonomic dysfunction was associated with both functional disability and depression in HD patients. Due to

the cross-sectional nature of our study, it is impossible to differentiate between cause and effect. However, autonomic symptoms are unlikely to be secondary to functional impairment, as by definition, autonomic functions are not under voluntary control. It is rather more likely that symptoms such as dysphagia, sialorrhea, and fecal and urinary incontinence could lead to social embarrassment, isolation and a negative impact on daily functioning. On the other hand, the relation between autonomic dysfunction and depression, which is also found in other patient populations,[20] is harder to explain since depression itself can be accompanied by several vegetative symptoms such us loss of libido.[23] In fact, depression was the only independent predictor of autonomic dysfunction in HD patients, indicating that its effect on autonomic symptoms is independent of, e.g., functional disability. Although antidepressant use was correlated with the extent of autonomic complaints in HD patients, adjustment for the severity of depressive symptoms rendered this relation insignificant, suggesting that the association between depression and autonomic dysfunction is unlikely to be secondary to medication. Longitudinal studies of autonomic symptoms are needed to more precisely delineate the temporal association between depression to autonomic dysfunction in HD.

There are no reasons to suspect damage to the peripheral nervous system in HD,[5-7] so the site of autonomic dysfunction is more likely found in the central autonomic network including the hypothalamus and its connections to the cortex, limbic system, brainstem and spinal cord.[24] Substantial hypothalamic pathology has indeed been found in both HD patients and animal models of the disease.[3,25] Recently, a significant loss of dopamine D_2 receptors as well as microglia activation was found in the hypothalamus of both HD patients and premanifest mutation carriers.[26] As these abnormalities as well as neuronal inclusions of mutant huntingtin were seen throughout the hypothalamus,[26,27] hypothalamic damage might account for the autonomic dysfunction that encompasses both sympathetic and parasympathetic functions.[4-7] Further studies combining autonomic functional tests with whole brain, and in particular hypothalamic, assessment are needed to more accurately pinpoint the sites of pathology within the central autonomic network in HD.

In conclusion, autonomic symptoms are highly prevalent in HD patients, may even precede the onset of motor signs, and are related to functional disability and depression.

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