Objective: To examine the autonomic nervous system functions in patients with Huntington disease.

Background: Although patients with Huntington disease frequently experience vegetative symptoms, it is not clear if there is dysfunction of the autonomic nervous system.

Methods: Sympathetic skin response (SSR) latency and amplitude from both palms and soles and R-R (heart rate) interval variation (RRIV) at rest and during the Valsalva maneuver were examined in 22 patients and 21 age-matched controls. Unified Huntington’s Disease Rating Scale scores were determined in all the patients.

Results: Our data are reported as means ± SEMs. The SSR latencies in patients (mean palm latency, 1835.8 ± 110.7 milliseconds; mean sole latency, 2625.3 ± 226.9 milliseconds) were prolonged compared with controls (mean palm latency, 1359.5 ± 28 milliseconds [P < .01]; mean sole latency, 2038.1 ± 44.9 milliseconds [P < .01] and amplitudes in patients (mean amplitude, 1063.1 ± 237.7 µV) were smaller compared with controls (mean amplitude, 1846.3 ± 251.2 µV [P < .05]). The RRIV in patients both at rest (mean RRIV in patients, 3.7% ± 0.4% vs controls, 9.7% ± 0.6% [P < .01]) and during the Valsalva maneuver (mean RRIV in patients, 6.3% ± 1.6% vs controls, 14.5% ± 1.2% [P < .01]) was lower compared with controls. Furthermore, the prolonged SSR latencies, smaller amplitudes, and lower RRIV in patients compared with controls closely correlated with the various components of the Unified Huntington’s Disease Rating Scale scores (total behavior score and SSR latency, R = 0.6 [P < .01]; total behavior score and SSR amplitude, R = −0.5 [P < .05]; total behavior score and RRIV, R = −0.4 [P < .05]; verbal fluency and SSR latency, R = −0.5 [P < .05]; verbal fluency and SSR amplitude, R = 0.5 [P < .05], verbal fluency and RRIV, R = 0.5 [P < .05]; total functional capacity and SSR latency, R = −0.6 [P < .01]; total functional capacity and SSR amplitude, R = 0.5 [P < .05]).

Conclusion: These results suggest that there is autonomic nervous system dysfunction in patients with Huntington disease.

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Huntington Disease (HD) is an autosomal dominant neurodegenerative illness with mutation of a specific gene (IT 15) on chromosome 4, characterized by disorders of movement, functional capacity, cognition, and behavior due to degeneration of the basal ganglia (caudate nucleus), cerebral cortex, brainstem, spinal cord, and hypothalamus. Pathologic involvement of the hypothalamus, dorsal vagal nuclei, intermediolateral column cells in the spinal cord, and the thalamus, and various clinical features of autonomic disturbance (such as excessive sweating, a defect in postural vasoregulatory mechanism, impairment of pharyngeal and esophageal stage in ingestion, eating disorders, a disturbance in micturition, and endocrine dysfunctions) have been observed in patients with HD. Although there is pathologic evidence for involvement of the cerebral cortex, thalamus, hypothalamus, brainstem, cerebellum, and spinal cord in patients with HD, whether it leads to dysfunction of the autonomic nervous system (ANS) is not clear. Therefore, we studied the ANS functions by performing sympathetic skin response (SSR) measurements and R-R (heart rate) interval variation (RRIV) at rest and during the Valsalva maneuver.

The main objective of this study was to investigate ANS functions in a group of patients with definite or probable HD. We examined the SSR, which measures the changes in voltage originating on the surface of the skin after electrical stimulation of a nerve (somatosensory) and is
SUBJECTS AND METHODS

SUBJECTS

Twenty-two patients (13 women and 9 men; mean age, 49 ± 3 years; age range, 19-72 years) who fulfilled the diagnostic criteria (definite or probable) for HD were studied; 16 had definite HD and 4 had probable HD. There were 2 asymptomatic subjects with positive genetic test results. The mean age of onset was 44 ± 3 years; age range, 5-68 years; and the mean time from the onset of symptoms to participation in the study was 6 ± 1 years; range, 1-20 years; in 2 asymptomatic patients there were 5 months and 12 months, respectively, from date of diagnosis to participation in the study. Nine patients were taking antidepressant medications (+, fluoxetine hydrochloride; 3, amitriptyline hydrochloride; 1, vanfamoxine hydrochloride; 1, sertraline hydrochloride). Four patients were taking haloperidol; 3, baclofen; and 1, clonazepam. There were 21 age-matched normal control subjects (13 men and 8 women; mean age, 45 ± 4 years; age range 29-86 years). One control subject was taking estrogen replacement; 1, oral contraceptives (norgestrol, estradiol); and 3, multivitamins. Informed consent was obtained from patients or spouses and control subjects after detailed explanation of the procedures.

SYMPATHETIC SKIN RESPONSE

Sympathetic skin responses from both hands and feet were studied using the standard method. In brief, the skin temperature was maintained at 32°C (ambient temperature, 20-22°C). A standard electromyographic active disc (10-mm) electrode was attached bilaterally to the palm or sole and the reference electrode and ground electrode to the dorsum of the hand or foot, respectively. An electromyograph (TECA Sapphire; TECA Corp, Pleasantville, NY) was used. The tibial nerve at the ankle contralateral to the recording site was stimulated with square-wave pulses of 0.2-millisecond duration and 60-mA intensity, which were delivered at irregular intervals of more than 1 minute to prevent habituation. Three recordings of SSR at more than 1-minute intervals from each site (palm and sole) were obtained. The best of the 3 with greater reproducibility and lower than 5% variability was selected as the representative SSR. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection and expressed in milliseconds. The amplitude was measured from the baseline to the negative peak and expressed in microvolts. The response was considered absent if no consistent voltage change occurred using a sensitivity of 50 µV per division after 3 trials at maximum stimuli intensity.

R-R INTERVAL VARIATION

All the patients with HD and normal controls were studied using the electromyograph (TECA Sapphire). In brief, recording electrodes (active, reference, ground) were applied to the left anterior chest wall. Using the triggering mode and delay line, 80 sweeps were obtained at rest, and the range in the R-R interval (minimum minus maximum) was measured. Similarly, the range of R-R interval was also measured during the Valsalva maneuver by asking the subject to blow through a mouthpiece attached to the sphygmomanometer and to maintain a pressure of 40 mm Hg for 15 seconds with continuous electrocardiographic recording. The mean R-R interval (a) was the average of the longest and shortest R-R intervals, and the range of R-R interval (b) was the difference between them. The RRIV was defined as a percentage of the average interval using the following formula: RRIV = (b/a) × 100

In all patients and controls the standard motor (peroneal, tibial) and sensory (sural) nerve conduction studies were performed. The tibial H reflex was obtained when the side-to-side difference between SSR latencies in the sole was more than 200 milliseconds or when there was an absence of SSR response on one or both sides to rule out L5, S1 root dysfunction as a cause of the SSR abnormality. Median motor nerve, median sensory nerve (palm-to-wrist, digit 1-to-wrist, palm-to-digit 3) conductions were studied when side-to-side differences in SSR latencies in both hands were more than 200 milliseconds or there was an absence of SSR on one or both sides to rule out carpal tunnel syndrome as the cause of the SSR abnormality.

All patients were questioned for symptoms suggestive of ANS dysfunction such as altered perspiration, dizziness, and/or bowel or bladder dysfunction. Blood pressure was measured in the supine and erect positions after standing for 2 minutes. A drop in systolic blood pressure of more than 20 mm Hg or a drop in diastolic pressure of more than 10 mm Hg on standing was considered abnormal.

UNIFIED HUNTINGTON’S DISEASE RATING SCALE

Unified Huntington’s Disease Rating Scale (UHDRS) scores were collected for all patients to assess 4 main domains of clinical performance and capacity: motor function, cognitive function, behavioral abnormalities, and functional capacity, as recommended by the Huntington Study Group.

DATA ANALYSIS

An unpaired t test was used to assess differences between patients (whole group) and controls for SSR latencies and amplitudes, RRIVs at rest and during the Valsalva maneuver, height, and age. Also, to evaluate the effects of various drugs on ANS function measurements, an unpaired t test was used to assess the difference between subgroup 1 (13 of the 22 patients taking drugs), subgroup 2 (9 of the 22 patients not taking drugs), and controls. A paired t test was used to assess the difference between the right-side SSR measurements (latency and amplitude obtained from the sole and palm) and the left-side SSR measurements in controls and patients (whole group). The Pearson product correlation coefficient was used to (1) determine the relationship between the various SSR measurements, RRIV at rest and during the Valsalva maneuver, and various UHDRS score components (total behavior score [TBS], verbal fluency [VF], symbol digit, Stroop total, total functional capacity [TFC], and motor score); and (2) assess the intercorrelation between the various components of UHDRS scores. Statistical significance of the correlation coefficient was determined using the t test statistics.

The data were not adjusted for multiple comparisons. Statistical significance for all analyses was defined as P<.05.
Table 1. Autonomic Nervous System Measurements*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Right-Palm Latency, ms</th>
<th>P</th>
<th>Left-Palm Latency, ms</th>
<th>P</th>
<th>Right-Sole Latency, ms</th>
<th>P</th>
<th>Left-Sole Latency, ms</th>
<th>P</th>
<th>Resting RRIV, %†‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 21)</td>
<td>1359.5 ± 28.0</td>
<td>…</td>
<td>1358.1 ± 30.3</td>
<td>…</td>
<td>2038.1 ± 44.9</td>
<td>…</td>
<td>1955.7 ± 55.5</td>
<td>…</td>
<td>9.7 ± 0.6</td>
<td>…</td>
</tr>
<tr>
<td>All patients (n = 22)</td>
<td>1835.8 ± 110.7</td>
<td>&lt;.001</td>
<td>1750.0 ± 64.9</td>
<td>&lt;.001</td>
<td>2625.3 ± 226.9</td>
<td>.008</td>
<td>2296.9 ± 96.0</td>
<td>.003</td>
<td>3.7 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subgroup 1† (n = 13)</td>
<td>1766.4 ± 113.9</td>
<td>&lt;.001</td>
<td>1717.5 ± 84.6</td>
<td>&lt;.001</td>
<td>2858.9 ± 401.7</td>
<td>.005</td>
<td>2394.4 ± 111.5</td>
<td>.005</td>
<td>3.5 ± 0.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subgroup 2‡ (n = 9)</td>
<td>1931.3 ± 217.0</td>
<td>&lt;.001</td>
<td>1798.8 ± 105.7</td>
<td>&lt;.001</td>
<td>2362.5 ± 153.3</td>
<td>.01</td>
<td>2271.4 ± 164.2</td>
<td>.01</td>
<td>3.9 ± 0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subgroup 1 vs subgroup 2</td>
<td>…</td>
<td>.52</td>
<td>…</td>
<td>.54</td>
<td>…</td>
<td>.29</td>
<td>…</td>
<td>.28</td>
<td>…</td>
<td>.59</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SEM; ellipses indicate not applicable.
†RRIV indicates R-R (heart rate) interval variation.
‡Subgroup 1 includes only patients taking drugs; subgroup 2 includes only patients not taking drugs.

used to evaluate central (preganglionic) and peripheral (postganglionic) sympathetic activity, and RRIV, which reflects the state of parasympathetic innervation to the heart. Our data are reported as means ± SEMs.

RESULTS

SYMPATHETIC SKIN RESPONSE

The SSR latencies and amplitudes are given in Table 1. The SSR latencies (both palms and soles) in patients (whole group and both subgroups) were significantly prolonged compared with controls (P<.01, Table 1). The SSR amplitudes in patients (whole group and both subgroups) obtained from palms were significantly smaller compared with controls (P<.05, Table 1), while the amplitudes from the soles were similar in both groups (P = .42, Table 1). The SSR responses were biphasic and latencies were shorter in hands compared with feet in controls and patients, as reported previously. The SSR latencies in the hands (1359.5 ± 28.0 milliseconds) and feet (2038.1 ± 44.9 milliseconds), the amplitude in the hands (1824.3 ± 251.2 µV) and feet (1224.4 ± 265.7 µV), and RRIVs (see below) in controls were similar to previously reported values.12-13

was a linear correlation between the right-sole latency and left-sole latency: R = 0.9, P<.01.

HEART RATE VARIABILITY (RRIV)

The RRIV data are given in Table 1. The RRIV in patients, both at rest and during the Valsalva maneuver, was significantly less than in controls (Table 1, P<.01) except in subgroup 2 (patients not taking drugs) during the Valsalva maneuver, which is suggestive of dysfunction of both the parasympathetic and sympathetic nervous systems in patients with HD. Two patients (9%) could not perform the Valsalva maneuver because of oral-lingual dysfunction in one and inability to follow instructions due to impaired cognition in the other. The RRIVs at rest and during the Valsalva maneuver were closely correlated in controls (R = 0.5, P = .02); on the other hand, there was no correlation between RRIVs at rest and during the Valsalva maneuver in patients (R = 0.2, P = 0.9), which indicates an imbalance between the parasympathetic and sympathetic control of the heart rate in patients with HD.

UNIFIED HUNTINGTON’S DISEASE RATING SCALE

The detailed characteristics of various components of the UHDRS scores of all the patients are as follows: mean motor score, 36.8 ± 5.6 (range, 0-93); VF, 19 ± 3.2 (range, 0-48); symbol digit, 25.1 ± 4.4 (range, 0-80); Stroop total, 117.7 ± 17.1 (range, 0-242); TBS, 17 ± 2.4 (range, 1-49); TFC, 9.1 ± 1.0 (range, 0-13). Nine patients (41%) were demented and 8 (36%) were depressed. These values indicate the spectrum of disease severity ranging from asymptomatic and mild to severe disability. Correlation analysis showed the 4 components of the UHDRS (TFC, cognitive functions [symbol digit, VF]; motor score, and TBS, in descending order) were significantly (R=0.5, P<.05) intercorrelated except Stroop total vs motor score (R = 0.2, P = .3) and TBS (R = 0.4, P = .08). There was also significant (R ≥ 0.4, P≤.05) correlation between the disease duration and various components of the UHDRS scores except for Stroop total (R = 0.4, P = .09) and symbol digit (R = 0.2, P = 0.7). These data indicate a high degree of internal consistency in each of the 4 components of the UHDRS.
ANS DYSFUNCTION: SUBJECTIVE AND OBJECTIVE

One patient (4.5%) complained of dizziness and had substantial postural hypotension (sitting blood pressure, 128/78 mm Hg; standing, 106/64 mm Hg). One patient (4.5%) had decreased sweating. One patient (4.5%) had marked weight loss (cachexia) and also had urinary incontinence. One patient (4.5%) had sexual dysfunction as a result of increased libido. These vegetative symptoms and signs suggest central autonomic network dysfunction. However, other conditions (depression, dementia, excessive abnormal motor activity) could also contribute substantially to the development of some of these vegetative symptoms. Furthermore, the discrepancy between the common observation of abnormalities of SSR and RRIV and the rare occurrence of clinical findings of failure of autonomous function in patients with HD, as seen in patients with multiple sclerosis and amyotrophic lateral sclerosis, is in agreement with the fact that degeneration of the ANS must be profound before clinical signs appear; abnormal clinical function could be masked by other disabilities and thus difficult to evaluate without specific testing.

STANDARD NERVE CONDUCTION STUDIES

The standard motor (peroneal, tibial) and sensory (sural, median) nerve conduction study results and tibial H reflexes were within the normal range in patients and controls, except that 4 patients (18%) and 5 controls (24%) had asymptomatic carpal tunnel syndrome. The measurements of these asymptomatic subjects (4 patients, 5 controls) were not excluded from the statistical analysis. There was no difference between patients’ height (171.0 ± 2.0 cm) and controls’ height (171.0 ± 2.0 cm, P = .3). The woman-man ratio in patients (13:9) was higher than in controls (8:13). Sex does not affect RRIV but the decline in sudomotor function with aging is slightly greater in elderly women (older than 65 years) than in men.

ANS MEASURES AND UHDRS ASSESSMENT

The correlation between various ANS measures and variables (subclasses) of UHDRS is given in Table 2. The SSR latency (both palms and soles) was closely correlated to TBS (Table 2), and was negatively correlated to symbol digit, TFC, VF (Table 2), and Stroop total in descending order. Similarly, SSR amplitudes (both palms and soles) were closely correlated to symbol digit, Stroop total, VF, TFC, and TBS (negatively, Table 2). These findings suggest that patients with greater impairment of cognitive functions and greater decline in TFC and behavioral functions had more abnormal (prolonged latencies, smaller amplitude) SSR responses (sympathetic dysfunction). Furthermore, RRIVs both at rest and during the Valsalva maneuver were closely correlated to symbol digit, Stroop total, VF (during the Valsalva maneuver), and TBS (negatively, during the Valsalva maneuver, Table 2), suggesting that patients with greater impairment of cognitive functions and greater decline in TFC and behavioral abnormalities had less variation of heart rate. In summary, patients with HD who had greater impairment of behavior, cognitive functions, and TFC had abnormal SSR responses (prolonged latencies, small amplitude, and absent responses) and had less variation of heart rate both at rest and during the Valsalva maneuver, indicating dysfunction of both sympathetic and parasympathetic components of the ANS.

<table>
<thead>
<tr>
<th>Valsalva</th>
<th>Palm</th>
<th>Sole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneuver</td>
<td>RRIV, %</td>
<td>P</td>
</tr>
<tr>
<td>14.5 ± 1.2</td>
<td>. . .</td>
<td>1846.3 ± 251.2</td>
</tr>
<tr>
<td>6.3 ± 1.6</td>
<td>&lt; .001</td>
<td>1063.1 ± 237.7</td>
</tr>
<tr>
<td>6.4 ± 1.3</td>
<td>&lt; .001</td>
<td>893.5 ± 234.1</td>
</tr>
<tr>
<td>9.0 ± 3.4</td>
<td>.06</td>
<td>822.0 ± 273.7</td>
</tr>
<tr>
<td>. . .</td>
<td>.39</td>
<td>. . .</td>
</tr>
</tbody>
</table>

The major findings of this study were as follows: (1) prolonged SSR latencies (in both palms and soles) and smaller SSR amplitudes (both palms) in patients with HD compared with controls; (2) absence of SSR in 8 patients (36%) compared with presence in all controls; (3) decreased RRIV both at rest and during the Valsalva maneuver (except in subgroup 2, P = .06) in patients with HD compared with controls; and (4) a significant positive correlation between the abnormalities of ANS function measurements (SSR latency and amplitude and RRIV) and abnormalities in measures of disease progression (various components of UHDRS and disease duration), which suggests that as the disease progresses, in addition to a decline in the functions of the basal ganglia (caudate), cerebral cortex, brainstem, and spinal cord, there is also a decline in functions of the central autonomic network (control center for sympathetic and parasympathetic system).

Further, findings from histopathologic studies of the central nervous system in patients with HD have shown involvement of primary or secondary sites of ANS functions: the hypothalamus, brainstem (dorsal vagal nuclei), cerebral cortex, thalamus, and intermediolateral column cells in the spinal cord.

The SSR includes 3 phases: (1) somatosensory myelinated afferents, (2) central coupling, and (3) efferent controlled output. The SSR abnormalities and significantly diminished RRIV observed in patients with HD are most likely a result of dysfunction of the central (preganglionic) coupling process or its efferent pathways (central autonomic network: the hypothalamus and its connection to the neocortex, the limbic system, brainstem, and spinal cord) as seen in multiple sclerosis, Parkinson disease, and amyotrophic lateral sclerosis, rather than a peripheral postganglionic disorder as seen in peripheral neuropathy or progressive autonomic failure. This conclusion is based on the following findings: (1) the results from the standard peripheral nerve conduction stud-
ies were normal in all the patients except those with asymptomatic carpal tunnel syndrome (4 patients [18%] vs 5 controls [24%]); (2) none of the patients had signs or symptoms suggestive of peripheral neuropathy; and (3) similar to our observations, other investigators\textsuperscript{5,10} have noted ANS dysfunction in patients with HD and attributed it to diminished input from higher centers to the intact brainstem sympathetic system\textsuperscript{10} and dysfunction of vasoregulatory activities of the caudate nuclei.\textsuperscript{7} Furthermore, there is a close correlation between the abnormalities of ANS function measurements (SSR latency and amplitude and RRIV) and abnormalities in central nervous system functions (UHDRS scores) of patients with HD. However, we did not evaluate the status of sweat glands and the integrity of the local nerve supply to them by using a subcutaneous ace-
tylcholine or a pilocarpine injection test.

**CONCLUSIONS**

Patients with HD have significant subclinical autonomic dysfunction, and these autonomic functions decline significantly as the disease progresses. The SSR and RRIV could be used as a measure to monitor the progression of the disease and also in treatment trials as a measure (marker) for the change in the disease status.

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