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Composite Autonomic Scoring Scale for Laboratory Quantification of Generalized Autonomic Failure

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An autonomic reflex screen, which consisted of a quantitative sudomotor axon reflex test, orthostatic blood pressure and heart rate response to tilt, heart rate response to deep breathing, the Valsalva ratio, and beat-to-beat blood pressure measurements during phases II and IV of the Valsalva maneuver, tilt, and deep breathing, was used to develop a 10-point composite autonomic scoring scale of autonomic function. The scheme allots 4 points for adrenergic and 3 points each for sudomotor and cardiovagal failure. Each score is normalized for the compounding effects of age and sex. Patients with a score of 3 or less on the composite autonomic scoring scale have only mild autonomic failure, those with scores of 7 to 10 have severe failure, and those with scores between these two ranges have moderate autonomic failure. The sensitivity and specificity of the method were assessed by evaluating the composite autonomic scoring scale in four groups of patients with known degrees of autonomic failure: 18 with multisystem atrophy, 20 with autonomic neuropathy, 20 with Parkinson's disease, and 20 with peripheral neuropathy but no autonomic symptoms. The composite scores (means ± SD) for these four groups, respectively, were as follows: 8.5 ± 1.3, 8.6 ± 1.2, 1.5 ± 1.1, and 1.7 ± 1.3. Patients with symptomatic autonomic failure had scores of 5 or more, those without symptomatic autonomic failure had scores of 4 or less, and no overlap existed in these groups. Thus, autonomic laboratory tests should be useful in grading the degree of autonomic failure.

Since the founding of the Mayo Autonomic Reflex Laboratory in 1982, my colleagues and I have developed a battery of noninvasive autonomic tests that are sensitive, specific, reproducible (coefficient of variation, 20% or less), standardized, and sufficiently straightforward to perform.[1,2] The noninvasive and quantitative nature of the tests, as well as their ability to evaluate several autonomic systems (postganglionic sudomotor, adrenergic, and cardiovagal), suggested the value of generating a quantitative composite score that could be used to describe the severity of autonomic failure and to monitor both the progression of disease and the response to treatment. Thus, we have developed a composite autonomic scoring scale. This report describes that scale and its validation in two groups of patients with central neurologic involvement and two groups with neuropathies. For both central and peripheral disorders, one group had symptomatic autonomic failure and the other did not.

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PATIENTS AND METHODS

Symptoms of autonomic failure were graded by using a previously described scale, with minor modifications:[3] absent = no autonomic symptoms; mild = impotence, obstinate constipation, or xerostomia but absence of symptomatic orthostatic hypotension except for the development of transient episodes due to medication known to cause orthostatic hypotension; moderate = symptomatic orthostatic hypotension sufficient either to affect activities of daily liv-

ing or to necessitate treatment or the presence of severe urinary problems (or both); and severe = severe and persistent orthostatic hypotension with insufficient response to therapy.

Four groups of patients were assessed (Table 1). Two groups had autonomic symptoms of at least moderate degree, and two groups had no symptoms or only mild autonomic symptoms.

Group 1: Multisystem Atrophy.—The 18 patients in group 1 had multisystem atrophy (such as the Shy-Drager syndrome). They had early and prominent autonomic failure in addition to extrapyramidal or cerebellar involvement (or both). Autonomic failure, including orthostatic hypotension, was the major complaint. All patients had at least moderate autonomic symptoms.

Group 2: Peripheral Neuropathy and Autonomic Failure.—Peripheral neuropathy was considered present when distal weakness and sensory deficit were confirmed by nerve conduction and electromyographic evidence of neuropathy. Symptoms of moderate or severe autonomic involvement were present in all patients in group 2. The causes of the autonomic neuropathies in these 20 patients were as follows: idiopathic, 9; Sjögren's syndrome, 4; diabetes, 3; amyloidosis, 2; paraneoplastic disease, 1; and cisplatin, 1.

Group 3: Parkinson's Disease.—Group 3 consisted of 20 patients with Parkinson's disease. All patients had at least two of the following cardinal signs: rest tremor, rigidity, and bradykinesia. Other systems were uninvolved or only minimally involved. At least some response to levodopa therapy was noted. Patients had either no or only mild autonomic symptoms.

Group 4: Peripheral Neuropathy but No Autonomic Symptoms.—The 20 patients in group 4 had evidence of a neuropathy and no autonomic symptoms. The causes of these nonautonomic neuropathies were as follows: idiopathic, 10; monoclonal gammopathy, 4; chronic inflammatory demyelinating polyradiculoneuropathy, 3; and inherited, 3.

Quantitative Sudomotor Axon Reflex Test.—The quantitative sudomotor axon reflex test was used to measure the responses from the postganglionic sympathetic sudomotor axon.[4,5] Responses were routinely recorded from the forearm, the lateral proximal aspect of the leg, the medial distal aspect of the leg, and the proximal portion of the foot over the extensor digitorum brevis muscle. The stimulus was iontophoresed acetylcholine, and the responses were recorded in a compartment of a multicompartmental sweat cell that was separate from the stimulus compartment. The "axon reflex" is mediated by postganglionic sympathetic sudomotor fibers.[6] Control values were derived from studies of 223 normal subjects who were 10 to 83 years old.[1]

Heart Rate Response to Deep Breathing and Valsalva Ratio.—Previously described techniques[4,5] were used to determine the heart rate response to deep breathing and the Valsalva ratio. During deep breathing (6 breaths/min), the heart rate range in response to forced respiratory sinus arrhythmia was determined. For the Valsalva maneuver, the subject, rested and recumbent, was asked to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is the ratio of the maximal to the minimal heart rate. Control values were based on findings in 157 healthy subjects who were 10 to 83 years old.[1]

Orthostatic Blood Pressure Recordings.—Beat-to-beat blood pressure was monitored with use of a continuous monitor (Finapres monitor, Ohmeda, Englewood, Colorado) and input into a computer console that displayed systolic, diastolic, and mean blood pressures continuously.[3,7] Blood pressure was also determined by using a sphygmomanometer cuff and mercury manometer over the brachial artery.

Scoring of Autonomic Failure.—The 10-point composite autonomic scoring scale for autonomic function was based on the autonomic reflex screen (Tables 2 and 3). The

Table 1.—**Sex and Age Distribution and Duration of Disease in Patients With Various Types of Autonomic Dysfunction**

Diagnosis	No. of patients	Sex		Age (yr; mean ± SD)	Duration of disease (yr; mean ± SD)
		M	F		
Multisystem atrophy	18	11	7	64.8 ± 8.0*	4.2 ± 4.4
Peripheral neuropathy and autonomic failure	20	11	9	51.5 ± 15.3	2.6 ± 4.7
Parkinson's disease	20	14	6	62.4 ± 7.8†	5.3 ± 6.0
Peripheral neuropathy but no autonomic symptoms	20	13	7	62.9 ± 13.5*	4.1 ± 3.8

Versus peripheral neuropathy and autonomic failure:
*$P<0.05$.
†$P<0.01$.

Table 2.—**Elements of the Autonomic Reflex Screen**

1. Quantitative sudomotor axon reflex test—one upper and three lower limb sites
2. Orthostatic blood pressure and heart rate response to tilt
3. Heart rate response to deep breathing
4. The Valsalva ratio
5. Beat-to-beat blood pressure measurements during the Valsalva maneuver, tilt, and deep breathing

autonomic reflex screen (Table 2) evaluated the severity and distribution of postganglionic sudomotor failure (the quantitative sudomotor axon reflex test), cardiovagal function (the heart rate response to deep breathing and the Valsalva ratio), and adrenergic function (the beat-to-beat blood pressure measurements in response to tilt and the Valsalva maneuver). The composite autonomic scoring scale (Table 3) allots 4 points for adrenergic and 3 points each for sudomotor and cardiovagal dysfunction—because of the greater effect of adrenergic failure, especially orthostatic hypotension, than other autonomic deficits on the patient. The composite scores were normalized for the compounding effects of age and sex and also incorporated the alterations in blood pressure during phases II and IV of the Valsalva maneuver.[7]

Statistical Analysis.—The data were analyzed by using analysis of variance, and specific groups were compared with use of the Student *t* test for paired data. Data were expressed as means ± SD, and *P* values of less than 0.05 were considered significant.

RESULTS

The ages of the four groups were well matched except for those with peripheral neuropathy and autonomic failure (Table 1), who were significantly younger than the other three groups. The durations of the disorders were not significantly different but tended to be briefer for peripheral neuropathy associated with autonomic failure.

Sudomotor Score.—The sudomotor scores for patients with multisystem atrophy, peripheral neuropathy and autonomic failure, Parkinson's disease, and peripheral neuropathy but no autonomic symptoms were 2.4 ± 0.8, 2.5 ± 1.1, 0.8 ± 1.0, and 0.6 ± 0.9, respectively (Fig. 1). The scores for patients with multisystem atrophy and peripheral neuropathy plus autonomic failure were significantly greater ($P<0.001$) than those for patients with Parkinson's disease and peripheral neuropathy but no autonomic symptoms. No significant difference was noted between the two groups with symptomatic autonomic failure (multisystem atrophy versus peripheral neuropathy and autonomic failure) or between the two groups without symptomatic autonomic failure (Parkinson's disease versus peripheral neuropathy but no autonomic symptoms).

Table 3.—**Laboratory Grading of Autonomic Failure***

Sudomotor index

1 = Single site abnormal on quantitative sudomotor axon reflex test *or*
Length-dependent pattern (distal sweat volume <1/3 of proximal value) *or*
Persistent sweat activity at foot
[On thermoregulatory sweat test, anhidrosis present but <25%]†

2 = Single site <50% of lower limit on quantitative sudomotor axon reflex test
[On thermoregulatory sweat test, anhidrosis 25-50%]†

3 = Two or more sites <50% of lower limit on quantitative sudomotor axon reflex test
[On thermoregulatory sweat test, anhidrosis >50%]†

Adrenergic index‡

1 = Phase II_e decrease of <40 but >20 mm Hg mean BP *or*
Phase II_l does not return to baseline *or*
Decrease in pulse pressure to ≤50% of baseline

2 = Phase II_e decrease of <40 but >20 mm Hg mean BP + phase II_l or IV absent

3 = Phase II_e decrease of >40 mm Hg + absent phases II_l and IV

4 = Criteria for 3 + orthostatic hypotension (systolic BP decrease of ≥30 mm Hg; mean BP decrease of ≥20 mm Hg)

Cardiovascular heart rate index

1 = HR_{DB} or VR mildly decreased (above 50% of minimum)

2 = HR_{DB} or VR decreased to <50% of minimum

3 = Both HR_{DB} and VR decreased to <50% of minimum

*BP = blood pressure; HR_{DB} = heart rate response to deep breathing; VR = Valsalva ratio.

†Could be substituted for results of quantitative sudomotor axon reflex test.

‡Phases refer to components of the Valsalva maneuver: II_e and II_l = early and late portions, respectively, of phase II.

Adrenergic Score.—The adrenergic scores for patients with multisystem atrophy, peripheral neuropathy and autonomic failure, Parkinson's disease, and peripheral neuropathy but no autonomic symptoms were 3.9 ± 0.5, 3.6 ± 0.8, 0.3 ± 0.4, and 0.5 ± 0.6, respectively (Fig. 1). As with the sudomotor scores, those for patients with symptomatic autonomic failure (multisystem atrophy and peripheral neuropathy plus autonomic failure) were significantly greater ($P<0.001$) than those for patients without symptomatic autonomic failure (Parkinson's disease and peripheral neuropathy but no autonomic symptoms). No significant difference was observed within groups for those with symptomatic autonomic failure or for those without symptomatic autonomic failure.

Cardiovagal Score.—The cardiovagal scores for patients with multisystem atrophy, peripheral neuropathy and autonomic failure, Parkinson's disease, and peripheral

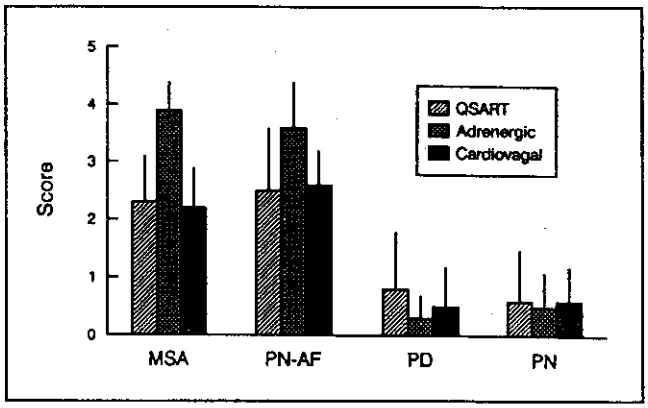

Fig. 1. Individual scores ± SD, normalized for age and sex differences, for quantitative sudomotor axon reflex test (*QSART*), adrenergic function, and cardiovagal function in patients with multisystem atrophy (*MSA*), peripheral neuropathy and autonomic failure (*PN-AF*), Parkinson's disease (*PD*), and peripheral neuropathy but no autonomic symptoms (*PN*).

neuropathy but no autonomic symptoms were 2.2 ± 0.7, 2.6 ± 0.6, 0.5 ± 0.7, and 0.6 ± 0.8, respectively (Fig. 1). The scores for patients with multisystem atrophy and peripheral neuropathy plus autonomic failure were significantly greater ($P<0.001$) than those for patients with Parkinson's disease and peripheral neuropathy but no autonomic symptoms. No significant difference was found between the two groups with symptomatic autonomic failure or between the two groups without symptomatic autonomic failure.

Composite Autonomic Scoring Scale.—The composite scores for patients with multisystem atrophy, peripheral neuropathy and autonomic failure, Parkinson's disease, and peripheral neuropathy but no autonomic symptoms were 8.5 ± 1.3, 8.6 ± 1.2, 1.5 ± 1.1, and 1.7 ± 1.3, respectively (Fig. 2). The scores for patients with multisystem atrophy and peripheral neuropathy plus autonomic failure were significantly greater ($P<0.001$) than those for patients with Parkinson's disease and peripheral neuropathy but no autonomic symptoms. No significant difference was noted between the two groups with symptomatic autonomic failure or between the two groups without such failure.

For the two conditions with symptomatic autonomic failure, 100% of patients had scores of 5 or more. Composite scores of 7 or more were found in 16 of 18 patients (89%) with multisystem atrophy and in 100% of those with peripheral neuropathy and autonomic failure. No patients in the two groups without symptomatic autonomic failure had a score that exceeded 4.

DISCUSSION

Certain key aspects of autonomic function can be measured noninvasively with precision, accuracy, and reproducibility in clinical laboratories. Autonomic failure is important to detect and quantify because it adversely affects function, is amenable to improvement, and may increase morbidity and mortality.[2] Some evidence suggests that the function of unmyelinated and small myelinated fibers may improve with treatment. Fagius and associates[8] found a statistically significant improvement in the heart rate response to deep breathing in patients treated with aldose reductase inhibitor and suggestive evidence of improvement in skin potentials in the foot.[8,9] My colleagues and I[10] found improvement in cholinergic function after treatment of the Lambert-Eaton myasthenic syndrome with 3,4-diaminopyridine. We[3] detected a correlation between the rate of progression and the degree of autonomic failure in the central autonomic disorders.

Another reason for undertaking autonomic evaluation is the poor prognosis of patients who have autonomic failure. Ewing and coworkers[11] suggested that autonomic failure, detected in cardiovascular heart rate tests, in association with the presence of clinical signs of autonomic dysfunction portended an extremely poor prognosis: 56% of 73 patients died in 5 years. In a recent study, Sampson and colleagues[12] found a less ominous prognosis in similar patients (but younger and without renal failure at the beginning of the study); the mortality was 25% at 10 years. The presence of a lengthening of the QT interval in patients with diabetes correlates with abnormal findings on clinical autonomic tests and has been suggested to contribute to unexpected death.[13,14] Patients with diabetes and impaired autonomic function may have increased instability of the blood pressure (that necessitates pharmacologic treatment) and increased intraoperative mortality.[15] Denervation supersensitivity is present in approximately 25% of patients with diabetic neuropathy.[16]

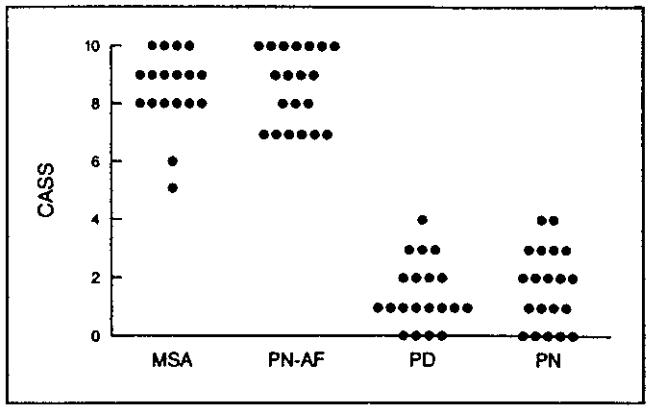

Fig. 2. Composite autonomic scoring scale (*CASS*) results for patients with multisystem atrophy (*MSA*), peripheral neuropathy and autonomic failure (*PN-AF*), Parkinson's disease (*PD*), and peripheral neuropathy but no autonomic symptoms (*PN*).

This phenomenon may result in dangerously high blood pressure responses when medications that contain phenylephrine hydrochloride or phenylpropanolamine hydrochloride are administered for coughs or colds. The same problem may occur in response to the local application or infiltrations of vasoactive agents—for example, injections of epinephrine or local anesthetic agents.

The main findings in the current study are that patients with central (multisystem atrophy) or peripheral neuropathy and symptomatic autonomic failure will be identifiable with the composite autonomic scoring scale with sensitivity and specificity and that patients without clinical autonomic failure, whether neurologic involvement is peripheral (peripheral neuropathy but no autonomic symptoms) or central (Parkinson's disease), will be easily separable from them without overlap. If a score of 7 or more is used as an index of severe autonomic failure, the test has a sensitivity of 94% and a specificity of 100%.

Of importance, the laboratory evaluation should be undertaken with tests of known sensitivity, specificity, and reproducibility, and these tests should be clinically relevant and noninvasive. The selected tests fulfill these criteria and have coefficients of variation of 20% or less.[2] A suggested criterion is that tests of autonomic function should evaluate at least three autonomic systems so that an adequate distribution of autonomic deficits is quantified.[17] The chosen battery measures the distribution and severity of postganglionic deficits, cardiovagal function, and both peripheral (α-) adrenergic and cardiac (β-) adrenergic functions. A more limited battery would be inadequate for at least two reasons. First, the autonomic system that is clinically relevant must be evaluated. For example, if a patient has a diabetic neuropathy and numbness of the feet, demonstrating impaired heart rate response to deep breathing provides no information on the limb nerves. Second, in the same patient, a 1 in 6 chance exists that the heart rate response to deep breathing and the quantitative sudomotor axon reflex test would yield discordant results.[18] The scoring system is slightly weighted to recognize the importance of adrenergic function by allocating 4 points to this aspect of the scale instead of the 3 points assigned to postganglionic sudomotor and cardiovagal functions. Another benefit of the evaluation is that it is adaptable. For instance, the percentage of anhidrosis on a thermoregulatory sweat test can be substituted for the distribution found on the quantitative sudomotor axon reflex test, and orthostatic hypotension (with a fixed heart rate) can be determined at the bedside. The suggested thermoregulatory sweat test substitutes are shown in Table 3. The scores relate to the severity of clinical autonomic failure. Grading autonomic failure by using autonomic laboratory tests should be possible (Table 4).

Table 4.—**Suggested Laboratory Grading of Autonomic Failure**

Composite autonomic scoring scale	Degree of autonomic failure
1-3	Mild
4-6	Moderate
7-10	Severe

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