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Cardiovascular and sweating dysfunction in patients with Holmes-Adie syndrome

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Abstract

A cross-sectional study is reported in which 53 patients with Holmes-Adie syndrome have been subjected to a battery of tests of autonomic nervous function referable to the cardiovascular system, to two objective tests of sweating function, and to subjective assessment of sweating by application of quinizarin powder followed by body heating. The majority of patients were consecutive referrals; none was selected because of clinical indications of autonomic dysfunction. Eighty three per cent of these patients had at least one, 57% at least two, and 40% at least three objective test abnormalities, as defined by values lying outside 95 percentiles of healthy subjects who were matched for age and subjected to the same tests. In the context of multiple testing, the probability of finding outside values was such that a minimum of 3 was required to define abnormality. On this basis 40% of patients were found to have significant evidence of autonomic dysfunction. The most frequent abnormalities were impaired digital vasoconstriction to cold (23%), a reduced heart rate response to the Valsalva manoeuvre (17%), and excessive variability in sweating between test sites (in one of the tests, 43%) which is consistent with patchy loss. Abnormal quinizarin test appearances were seen in 10 patients and in a further five patients the appearances were thought to be suggestive of abnormality. Though assessment of the results of this test are subjective, the observations are consistent with the findings obtained from the objective tests which were applied. Cardiovascular and sweating abnormality did not concur significantly and only the former was found to increase progressively with known duration of the pupillotonia. It is concluded that Holmes-Adie syndrome is commonly accompanied by progressive mild but widespread autonomic involvement but rarely is this symptomatic. If symptoms suggestive of autonomic neuropathy are found in a patient with tonic pupils, a careful search for some other generalised disorder is recommended.

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Holmes-Adie syndrome is widely recognised as comprising unilateral or bilateral tonic pupils with light-near dissociation together with tendon areflexia. Though the condition is almost always benign, a number of patients have been reported in whom disturbances of autonomic function occurred who could share the same unidentified aetiology. Thus, orthostatic hypotension,[1–4] cough syncope,[5] and impairment of cardiac vagal reflexes[6 7] are documented, suggesting that sympathetic and parasympathetic lesions may at least occasionally accompany this condition. Alternatively, as suggested by several authors, a putative lesion may lie within afferent fibres. Two patients with orthostatic hypotension described by Johnson *et al*[3] were found to have afferent baroreceptor blockade, which is consistent with this hypothesis. Such a finding may be analogous to the disturbance observed in H reflex function.[8]

Disturbance of sweating was first observed by Ross.[9] He reported the case of a 32 year old patient with Holmes-Adie syndrome who, in suffering from selective progressive sudomotor loss, readily developed heat intolerance. The association with Holmes-Adie syndrome he considered to be fortuitous but a number of further reports followed.[2 10–17] The occurrence of orthostatic hypotension in at least one of these cases[2] suggests that the sweating disorder is determined by damage to the controlling sympathetic nerve supply, though we know of no direct evidence that establishes this with certainty. Progressive hypohidrosis is likely to present clinically in one of two ways. Firstly, the affected skin areas may develop signs of drying. Secondly, if the anhidrotic area becomes very extensive, then hyperhidrosis will develop in the unaffected areas, particularly in hot climates and/or in response to exercise and body heating. Such hyperhidrosis is, however, likely to be a late manifestation of a progressive disorder of this type and it is therefore possible that lesser degrees of sweating disturbance may exist undetected in this condition.

Autonomic involvement in Holmes-Adie syndrome has been reviewed by Johnson.[18] Though it is clear that autonomic function may be disturbed, we cannot find documented evidence to indicate the prevalence of such disturbances in this condition. The present study has been undertaken to investigate the prevalence of cardiovascular reflex and

sweating disturbance in patients with Holmes-Adie syndrome, as judged by responses to a battery of tests.

Methods

PATIENTS AND HEALTHY SUBJECTS

Fifty three patients were recruited to the study; 43 were consecutive referrals from St Thomas' Hospital, Moorfields Eye Hospital, and the National Hospital for Neurology and Neurosurgery, London. Ten further patients, whose names were on a diagnostic register, were studied at the Iowa State University Hospital, Iowa City, USA. None was selected or referred because of known abnormalities of the autonomic nervous system other than pupillotonia and none had symptoms indicative of cardiovascular autonomic abnormality as revealed by direct questioning. One patient, a 39 year old man, reported a six year progressive history of excess sweating on the left side of the body sufficient on occasion to produce marks of salt deposition on that trouser leg and shoe; much of his right side he described as excessively dry. This patient undoubtedly had Ross's syndrome. No other patient admitted to a sweating abnormality.

Cohorts of a parallel group of 71 healthy subjects of approximately matching age and sex distribution were studied for comparison; the numbers studied are provided in the Results section. None of the patients or healthy subjects was taking drugs which had action on the autonomic nervous system. Characteristics of both groups are given in table 1.

All subjects gave written consent to participation and the study was approved by the ethics committee of West Lambeth Health Authority.

DIAGNOSIS

The diagnosis of Holmes-Adie syndrome was based on unilateral or bilateral pupillotonia as recorded by a Whittaker infrared television pupillometer, on light-near dissociation and, where light reflex response remained, on segmental iris palsy. Seventeen patients had bilateral involvement. Tendon jerk hyporeflexia was present in all but four patients. Each subject had a normal fasting blood sugar and glucose tolerance test, negative VDRL, normal peripheral vibration sense (as recorded by biothesiometer), and was free from other neurological, orbital, or ocular disease.

Table 1 Characteristics of healthy subjects and patients with Holmes-Adie syndrome

	Healthy	*Holmes-Adie*
n	71	53
Sex (M/F)	34/37	13/40
Age:		
(median)	43	42
(range)	20–84	25–80
Systolic BP (mm Hg)*	126 (24)	118 (21)
Diastolic BP (mm Hg)*	72 (12)	69 (9)
Heart rate (bpm)*	67 (11)	66 (10)
Pupillotonia:		
Known duration (years)		
median	-	9
range	—	0·5-42
Unilateral/bilateral	—	36/17

*Mean (standard deviation).

INVESTIGATIONS

Six tests of cardiovascular autonomic function were applied as follows. Resting cardiac sinus arrhythmia and the response to deep breathing and a Valsalva manoeuvre were recorded with a microcomputer linked ECG.[19] Systolic and diastolic blood pressure and heart rate responses to slow passive head-up 70° tilt were measured by sphygmomanometry and ECG respectively. The response to sustained hand grip to 30% of maximum voluntary contraction was measured similarly.[20] The digital blood flow response to opposite hand immersion in ice-cold water was recorded by plethysmography (Vasculab SPG16) with the strain gauge applied to the middle phalanx of the left index finger. The response was calculated as proportional reduction in flow.

Three tests of sweating were applied to 51 of the patients (two declined to be tested) in the following order. Skin resistance was recorded with surface electrodes applied to the first digit of each limb, using a microammeter linked to a BBC B computer. Measurements (in kohms) were taken from all four sites at rest (baseline) and in response to a single deep breath (psychogalvanic response). The latter was recorded as percentage change in resistance. Baseline values for the four sites were averaged and expressed as a mean value and the variability between sites as the coefficient of variation (CV% = SD × 100/mean). The psychogalvanic responses were expressed in the same way. The numbers of active sweat glands at two sites (1 cm diameter) on the volar aspect of each forearm were recorded with a plastic impression technique.[21] The proximal site was at the junction of the upper and middle thirds, the distal site at the junction of the middle and lower thirds. Measurements were taken from all four sites at rest (baseline) and following intradermal injection of carbachol (2×10^{-5}M; 0·183 μg in 0·05 ml). As with resistance measurements, the results were expressed as mean and CV%. Finally, body sweating was assessed subjectively following dusting the skin of the trunk, shoulders, and upper limbs with quinizarin red powder and raising of core temperature by 1°C by immersion of both legs to knee level for 20 minutes in a water bath maintained at 43°C. The results were graded as abnormal if there was asymmetric patchy loss, and doubtful if there appeared to be symmetric patchy loss.

STATISTICAL ANALYSIS

All test results on patients were compared with age-related normal values previously published (cardiac sinus arrhythmia, deep breathing, and Valsalva responses) or with values obtained on the healthy subjects studied here. Where appropriate, these were calculated as deviations from, or as ratios to, the expected values. Abnormal test results were

Table 2 Cardiovascular function test results (mean and SEM) in healthy subjects and patients with Holmes-Adie syndrome

		Healthy subjects Mean	95%		Holmes-Adie patients Mean	No abnormal		Difference between groups	
Measurement	n	(SEM)	CI	n	(SEM)	(high)	(low)	t test	p value
Sinus arrhythmia and related:									
Mean RR interval (ms)		898	655–1141	52	908(19)	3	1	0·520	0·605
SD of RR interval (O/E)*		1·0	0·41–2·44	52	0·86 (0·05)	0	1	−2·768	0·008
Deep breathing difference (O/E)*		1·0	0·38–2·61	52	1·14 (0·07)	2	1	1·890	0·064
Valsalva ratio (O/E)*		1·0	0·36–2·77	52	0·79 (0·08)	1	9	−2·670	0·010
Hand grip changes:									
Diastolic BP (mm Hg)	37	21·8 (1·3)	5–38	52	20·6 (1·3)	2	3	−0·630	0·530
Heart rate (bpm)	37	14·9 (1·2)	0–30	51	18·0 (1·5)	6	2	1·480	0·142
Digital blood flow:									
Proportional reduction	32	0·59 (0·03)	0·24–0·93	51	0·47 (0·04)	0	12	−2·213	0·030
Tilt test changes:									
Systolic BP (mm Hg) (O/E)*	65	0	(−)20-20	43	1·0 (1·7)	2	1	0·604	0·549
Diastolic BP (mm Hg) (O/E)*	65	0	(−)15-15	43	−2·7 (1·0)	0	3	−2·620	0·012
Heart rate (bpm) (O/E)*	65	0	(−)12-12	42	3·6 (1·2)	6	0	2·882	0·006

*O = observed; E = expected (age-dependent); 95% confidence intervals are approximate.

defined as values lying outside 95 percentiles in the normal range.

Grouped deviations from the expected values and differences between patient and healthy groups were tested by Student's unpaired *t* tests. Relationships between test results and known duration of pupillotonia were examined by linear regression analysis using standard methods.

Results

The mean results of all the tests applied to healthy subjects and Holmes-Adie patients are given in tables 2 and 3. The differences between groups are presented as unpaired *t* tests and the numbers of patients lying outside the normal confidence limits are provided.

SINUS ARRHYTHMIA AND RELATED TESTS

All but two of the patients had resting heart rates within the normal range. These two, women aged 44 and 58 years, had no other abnormal results. One patient, a 66 year old man known to have had pupillotonia for 17 years, had reduced sinus arrhythmia at rest and on forced deep breathing, as well as an abnormally low Valsalva ratio. Eight further patients (one man, seven women) had abnormally low Valsalva ratios (fig 1). As a group the patients yielded significantly lower values of resting sinus arrhythmia (0·86 vs 1·00, p = 0·008) and of the Valsalva ratio (0·79 vs 1·00, p = 0·010).

HAND GRIP CHANGES

The responses of the patients to sustained hand grip did not differ significantly from those of the healthy subjects. Five patients showed diastolic BP changes outside the normal range, two above and three below, and seven patients had heart rate changes outside the normal range, five above and two below. Such a distribution pattern is of doubtful significance.

DIGITAL BLOOD FLOW

The patients with Holmes-Adie syndrome had a significantly reduced response of digital blood flow to ice-cold hand immersion by comparison with the healthy subjects (0·47 vs 0·59, p = 0·030). Twelve of the patients (three men, nine women) showed responses below the normal range (fig 1).

TILT TEST CHANGES

The responses of the patients to passive head-up tilt differed marginally from those of the healthy subjects. Systolic BP changes did not differ, but diastolic BP fell slightly more (−2·7 mm Hg, p = 0·012) and the heart rate rose

Table 3 Sweat test results (mean and SEM) in healthy subjects and patients with Holmes-Adie syndrome

		Healthy subjects Mean	95%		Holmes-Adie Patients Mean	No abnormal		Difference between groups	
Measurement	n	(SEM)	CI	n	(SEM)	(high)	(low)	t test	p value
Skin resistance (kohms)									
Mean baseline	35	513 (58)	0–1200	48	816 (128)	6	0	1·920	0·058
CV%* baseline	35	14·1 (1·6)	0–32·5	48	27·0 (3·5)	15	0	2·996	0·004
Mean psychogalvanic response	35	5·5 (0·8)	0–15	48	5·9 (0·6)	2	0	0·397	0·692
CV% psychogalvanic response	35	30·4 (2·8)	0–64	47	49·7 (4·8)	14	0	3·181	0·002
No of active sweat glands									
Mean baseline	31	5·1 (0·5)	0–11·1	47	9·8 (2·5)	7	0	1·488	0·141
CV% baseline	31	66·0 (5·5)	4·3–127·8	47	66·6 (5·0)	3	0	0·077	0·939
Mean carbachol stimulated	31	89·9 (5·5)	28·4–151·5	47	87·9 (5·0)	3	0	0·267	0·790
CV% carbachol stimulated	31	28·3 (2·0)	5·8–50·8	47	38·6 (2·6)	10	0	2·839	0·006

CV% = coefficient of variation.

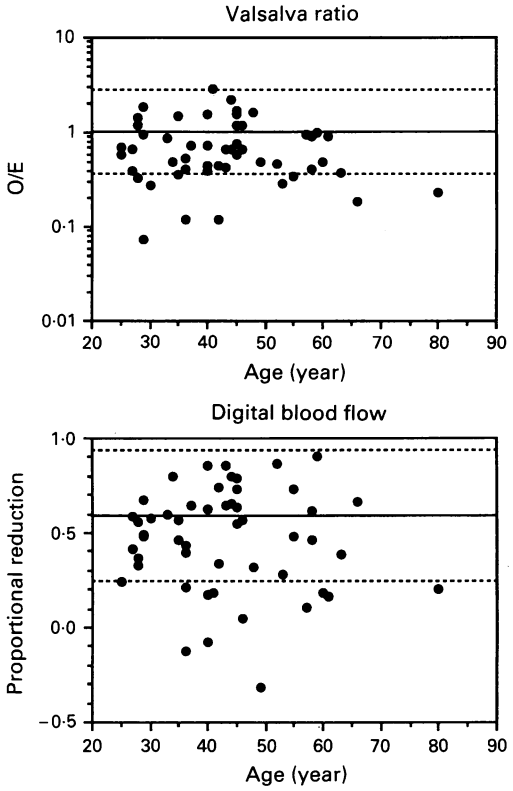

Figure 1 The Valsalva ratio (A), expressed in relation to the age-related normal value,[19] and the proportional reduction in digital blood flow induced by cold water immersion of the opposite hand (B) in patients with Holmes-Adie syndrome in relation to age. Continuous lines indicate mean values in healthy subjects. Broken lines indicate the upper and lower 95 percentiles of the normal range.

slightly more (3·6 bpm, p = 0·006) than expected. Six patients (four men, and two women) had heart rate changes above the normal range.

SKIN RESISTANCE (FIG 2)

In the healthy subjects, there were no significant differences in mean resistance or psychogalvanic response between the four test sites used. The mean baseline skin resistance in the patients was marginally higher (p = 0·058) than in the healthy subjects and this was subject to significantly greater variability as indicated by the CV% (p = 0·004). The mean psychogalvanic response of the patients did not differ from that of the healthy subjects, but it was subject to significantly greater variability (p = 0·002). In both cases, the greater variability is indicative of patchy functional differences.

FOREARM SWEAT GLAND COUNTS (FIG 3)

In the healthy subjects, there were significantly greater numbers of active sweat glands at the distal than at the proximal forearm test sites, both at baseline (5·9 vs 4·3, p = 0·009) and after carbachol stimulation (103·8 vs 76·1, p < 0·001), but there were no significant side to side differences in either measurement. The mean number of active sweat glands in the patients did not differ from that in the healthy subjects at baseline (p = 0·141) nor after carbachol stimulation (p = 0·790). The numbers of sweat glands activated by carbachol was, however, subject to significantly greater variability as indicated by the CV% (p = 0·006). In this case, the greater variability is indicative of a patchy functional difference.

QUINIZARIN TESTS

Ten patients showed evidence of patchy asymmetric sweating loss; this group included the one patient who had symptomatic localised hyperhidrosis as described in the Methods section. Five further patients also appeared to have patchy loss but in these cases the loss was symmetrical and to that extent it must therefore be regarded as uncertain.

PATIENTS WITH ABNORMAL RESPONSES

In the tests performed 44/53 patients (83%) had at least one abnormal result, 30 patients

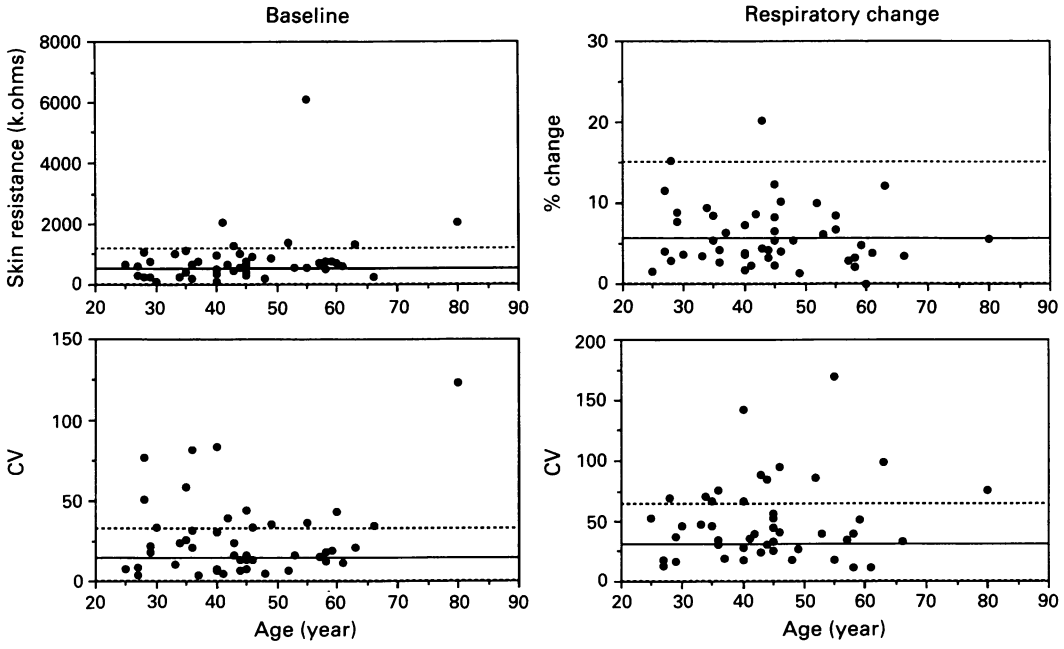

Figure 2 Mean skin resistance, its percentage change with deep respiration, and their variability between test sites (CV) in patients with Holmes-Adie syndrome. Symbols as in figure 1.

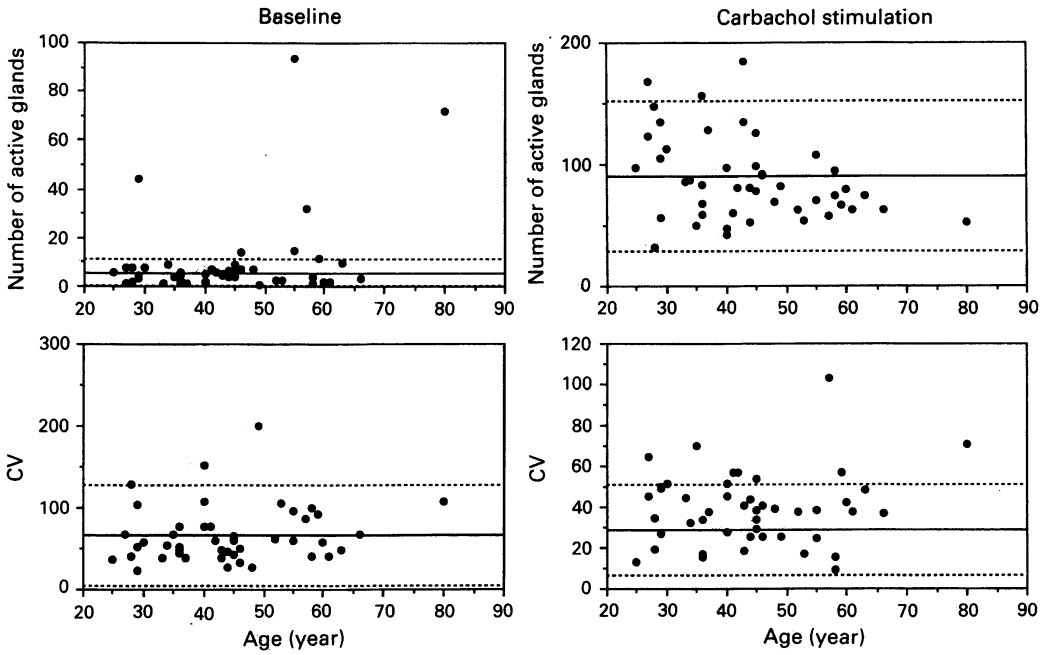

Figure 3 Mean number of active sweat glands at baseline, after carbachol stimulation, and their variability between test sites (CV) in patients with Holmes-Adie syndrome. Symbols as in figure 1.

(57%) had at least two, and 21 patients (40%) at least three abnormal results. Two patients, a 28 year old woman and a 55 year old woman, each had five abnormalities, one 40 year old man had six, and one 80 year old man seven abnormal test results. Assuming a binomial distribution of test abnormalities, the probability of these findings occurring solely from multiple testing is $p < 0{\cdot}001$ ($\chi^2 = 256{\cdot}00$). With the number of tests applied in this study, however, the overall probability that results outside the normal 95 percentiles will be found is such that only a minimum of three or more such results in the individual patient can be taken as evidence of his or her abnormality. On this basis 21 patients (40%) have evidence of autonomic dysfunction. There was no sex bias in the occurrence of abnormal test results.

The commonest abnormal findings were (a) a reduced Valsalva response; (b) reduced digital vasoconstriction in response to cold; and (c) exaggerated variabilities in three of the sweating tests. An abnormal Valsalva response occurred in 8/21 patients who had at least three abnormal test results and in only 1/32 patients who had fewer. As a predictor of multiple abnormality indicating autonomic dysfunction as defined above, this test has sensitivity of 38·1% and specificity of 96·9%. Similarly, the digital blood flow test showed sensitivity of 38·1% and specificity of 87·5%. Variation in baseline skin resistance showed sensitivity of 61·9% and specificity of 93·7%

An abnormal appearance on quinizarin testing occurred in 11/21 patients who had at least three abnormal objective test results and in only 4/30 patients who had fewer. As a predictor of multiple abnormality, this test has sensitivity of 52·4% and specificity of 86·7%.

The duration of pupillotonia was known in 41 patients, there being borderline association between increased duration and involvement of the second eye (Spearman $r = 0{\cdot}313$, $p = 0{\cdot}046$). Increased duration was associated marginally with a decline in the Valsalva ratio ($p = 0{\cdot}080$), and with a fall in heart rate response to hand grip ($p = 0{\cdot}022$), a fall in digital vasoconstriction to cold ($p = 0{\cdot}005$), an increase in resting skin resistance ($p = 0{\cdot}023$) and its variability ($p = 0{\cdot}035$), a decrease in the response of sweat glands to carbachol stimulation ($p = 0{\cdot}003$), and a borderline increase in its variability ($p = 0{\cdot}085$) (table 4). The prevalence of all test abnormalities increased with increasing duration of the condition (Spearman $r = 0{\cdot}331$, $p = 0{\cdot}034$), though this relationship was found only with the cardiovascular tests ($r = 0{\cdot}364$, $p = 0{\cdot}019$) and not with the sweating tests ($r = 0{\cdot}170$, $p = 0{\cdot}287$). Overall, the prevalence of cardiovascular abnormalities did not correlate significantly with that of sweating abnormalities ($r = 0{\cdot}214$, $p = 0{\cdot}131$).

Table 4 Cardiovascular and sweating tests results in patients with Holmes-Adie syndrome. Relationship with known duration of pupillotonia (n = 41)

Measurement	*Slope (per 10 years)*	*t test*	*p Value*
Sinus arrhythmia and related:			
Mean RR interval (ms)	−30·5	−1·468	0·150
SD of RR interval (O/E)	−0·02	−0·365	0·717
Deep breathing difference (O/E)	−0·03	−0·317	0·753
Valsalva ratio (O/E)	−0·14	−1·800	0·080
Hand grip changes:			
Diastolic BP (mm Hg)	−1·22	−0·903	0·372
Heart rate (bpm)	−4·11	−2·399	0·022
Digital blood flow:			
Proportional reduction	−0·12	−2·971	0·005
Tilt test changes:			
Systolic BP (mm Hg) (O/E)	−2·3	−1·389	0·175
Diastolic BP (mm Hg) (O/E)	−1·2	−0·990	0·330
Heart rate (bpm) (O/E)	−2·2	−1·532	0·137
Skin resistance:			
Mean	140·5	2·389	0·023
CV%	9·1	2·197	0·035
Mean respiratory change	−0·73	−1·080	0·288
CV% respiratory change	−1·8	−0·382	0·705
Active sweat glands:			
Mean unstimulated	5·4	1·671	0·104
CV% unstimulated	9·3	1·589	0·122
Mean stimulated	−17·5	−3·236	0·003
CV% stimulated	5·3	1·773	0·085

Discussion

The observations reported here indicate that disturbance in autonomic function as revealed by a battery of cardiovascular and sweating test responses is common in patients with Holmes-Adie syndrome. Thus, we found in this cross-sectional study that 83% showed at least one, 57% at least two, and 40% at least three test abnormalities. This high prevalence of abnormal test results must, however, be interpreted in the knowledge that with multiple tests (normal range defined as the mean with 2 SDs), the probability of obtaining outlying results is very high. Taking this into account, we conclude that 40% of the subjects show evidence of abnormality. The most frequent such abnormalities involved impaired peripheral vasoconstriction in response to cold, a reduced heart rate response to the Valsalva manoeuvre, and excessive variability in sweating tests. Overall, approximately equal numbers of subjects had evidence of cardiovascular and sweating disorder. Our findings are therefore consistent with the few existing published clinical reports of autonomic dysfunction in this condition, though they indicate that the underlying abnormalities are probably more frequent than previously supposed.

We failed, however, to observe a clear distinctive pattern of disorder which could permit localisation to a particular part of the autonomic nervous system. Failure of peripheral vasoconstriction and abnormal sweat gland responses imply that the sympathetic system is involved; failure to slow the heart during the recovery phase of the Valsalva manoeuvre, as previously reported,[6] implies parasympathetic involvement. We found an abnormally low Valsalva ratio in nine (17%) of our patients, which is consistent with impaired parasympathetic function, and in a few other patients exaggerated heart rate responses to hand grip and passive upright tilt which are also possible consequences of disturbed parasympathetic function. Such considerations suggest that on the efferent side both divisions of the autonomic nervous system may be involved in Holmes-Adie syndrome, though the integrated and interactive nature of their function in normal physiology makes this deduction uncertain. The disorder would also appear to be consistent with an abnormality lying within autonomic afferents, to which reference was made earlier, though our observations do not help to distinguish this possibility.

The prevalence of cardiovascular abnormalities observed, collectively and in some individual tests, was found to increase with increasing known duration of pupillotonia. Thus, among the 10 patients who were known to have had the condition for 15 years or more, nine of them had at least one, and five had at least two test abnormalities. This suggests that involvement of the autonomic nervous system is progressive. Despite this general picture, however, not one of the patients had symptoms referable to this involvement. If the disturbances observed are indicative of an autonomic neuropathic process analogous to that affecting the ciliary ganglia, it must be one which is characterised by very slow progress. It can be concluded that cardiovascular reflexes are frequently impaired in Holmes-Adie syndrome, which is suggestive of progressive autonomic dysfunction in this condition. The impairment, however, rarely results in clinical disturbance. It follows that, if symptoms indicative of autonomic neuropathy are found in a patient with tonic pupils, a careful search for a generalised cause must be instituted.

The observations reported here indicate that disturbance of sweating as revealed by measurement of skin resistance and counting of active sweat glands is also common in patients with Holmes-Adie syndrome. Thus, we found in this cross-sectional study that 61% showed at least one and 37% at least two such test abnormalities. Skin resistance has long been employed as a measure of sweating but is prone to great inter and intra-subject variation. As expected, therefore, our observed normal ranges for baseline resistance and for the psychogalvanic response were wide. In each case the 95% confidence intervals embraced zero, making it impossible to detect reduced resistance—that is, hyperhidrosis, with this test. Six patients, however, had increased baseline resistance, indicating areas of hypohidrosis, and larger numbers showed exceptionally wide variations in sweating between the various test sites, both at baseline and in the psychogalvanic response, which is consistent with patchy sweating loss. Similar, though opposite, constraints affect the usefulness of testing the numbers of active sweat glands within discrete areas of forearm skin. Nevertheless, six patients showed exaggerated responses to this test, four of them by a substantial margin (fig 3). As expected, larger numbers showed exceptionally wide variations in sweating between the various test sites, which is consistent with patchy involvement of the sudomotor system.

These findings are consistent with the appearances obtained when these patients were subjected to quinizarin testing, the assessment of which is less objective. We were indeed surprised that as many as 10 of the patients had obvious asymmetric, and a further five less obvious symmetrical, sweating loss. In the analysis, however, this served to confirm the objective evaluations which indicate a remarkably high prevalence of sweating impairment in this condition.

It has been suggested that sweating loss in Ross's syndrome is caused by autonomic nerve dysfunction.[2] On this basis we had anticipated that the occurrence of sweating loss in these patients would coincide with autonomic dysfunction affecting the cardiovascular system and furthermore that it would be related to the duration of pupillotonia. No such association was apparent in the analysis and there is therefore no present basis for the assumption that the sweating and cardiovascular abnormalities are necessarily manifesta-

tions of the same general disturbance. It can be concluded that sweating is frequently impaired in Holmes-Adie syndrome, though the development of symptomatic hypohidrosis as first described by Ross[9] must still be regarded as a rarity.

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