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Autonomic function in Holmes Adie Syndrome

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Summary

Autonomic function was studied in a group of 11 patients with Holmes Adie Syndrome. Autonomic function was assessed by the measurement of cardiovascular reflexes. Heart rate responses to respiration, valsalva manoeuvre and standing were studied. The change in systolic blood pressure on moving from the lying to the standing position was measured. Abnormalities of parasympathetic function were found in three patients, compared with matched controls. Autonomic dysfunction in Holmes Adie Syndrome may be more widespread than previously suspected.

Holmes Adie Syndrome is characterised by loss of deep tendon reflexes and a tonic pupillary reaction.[1,2] The tonic pupil comprises an absent or segmental response to light, a tonic near response and disturbances of accomodation.

Tonic pupils occur in a number of other conditions, and may be seen in patients with autonomic neuropathy. Holmes Adie Syndrome is, however, regarded as a benign condition, occurring in otherwise healthy patients.[3]

The aetiology of Holmes Adie Syndrome is unknown. It may be caused by as low virus.[4] The characteristic pupillary abnormality is due to parasympathetic post ganglionic denervation.[5] Histology shows an indolent degeneration of nerve cells in the ciliary ganglion, and suggests this is the site of the lesion.[6]

This study aimed to establish if there are more widespread abnormalities of the autonomic nervous system in patients with Holmes Adie Syndrome. The autonomic nervous system was assessed by the measurement of cardiovascular reflexes.

Patients and Methods

Patients with Holmes Adie syndrome seen at the Royal Victoria Hospital over five consecutive months were enrolled in the study. Written, informed consent was obtained from all patients and the study was approved by the Research Ethical Committee of the Faculty of Medicine, The Queen's University of Belfast.

Eleven patients with Holmes Adie Syndrome were studied. There were eight women and three men, aged 30 to 83 (mean 51) years. All patients has symptoms related to the pupillary abnormalities (Table I). The duration of symptoms ranged from two months to 30 years. None of the patients had any other symptoms of autonomic dysfunction.

All patients had a typical tonic pupillary response, and demonstrated supersensitivity to 0.1% pilocarpine. Two cases were bilateral. Nine of the 11 patients demonstrated loss of deep tendon reflexes. Full blood count, random blood sugar and syphilis serology were normal in all patients. Patients with diabetes or those taking autonomic drugs were excluded.

Eleven age and sex matched healthy con-

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Table I *Ocular symptoms in eleven patients with Holmes Adie Syndrome.*

	Number of Patients
Symptoms due to sphincter dysfunction	
Anisocoria	7 (64%)
Photophobia	8 (73%)
Difficulty with dark adaptation	4 (37%)
Symptoms due to ciliary muscle dysfunction	
Brow Ache	5 (45%)
Blur for near	7 (64%)
Blur for distance	4 (37%)

trols were also studied. Holmes Adie Syndrome and diabetes had been excluded in this group.

Cardiovascular autonomic function was assessed by four of the tests described by Ewing and Clarke.[7] The heart rate response to deep breathing at six breaths a minute, the valsalva manoeuvre and adopting the standing position was measured. The change in systolic blood pressure on standing, was recorded. Heart rate was measured via a three lead electrocardiogram and Hewlett-Packard 78203C heart rate monitor interfaced with an Apple II E microcomputer programmed to record and measure successive individual R-R intervals.[8] Thus resting heart rate and its coefficient of variation over 512 beats, and the heart rate responses to deep breathing, valsalva and standing could be accurately measured. The change in systolic blood pressure on changing from the lying to standing posture was measured by auscultation over the brachial artery.

Results

Normal, borderline and abnormal responses to tests of sympathetic and parasympathetic function were as defined by Ewing and Clarke[7] (Table II).

Table III shows the results of the tests of parasympathetic function for all 11 patients with Holmes Adie Syndrome, and some of the relevant clinical details. Table IV shows the results of the tests of parasympathetic function for all 11 controls.

Of the group with Holmes Adie Syndrome, seven of the patients had normal responses to all three tests of parasympathetic function. Patient five had a borderline heart rate response to deep breathing and standing. She was unable to perform the valsalva manoeuvre. Patient seven had an abnormal deep breathing response. Patient eight had abnormal deep breathing and valsalva responses. Patient nine had an abnormal deep breathing response.

Ten of the control group had normal responses to all three tests of parasympathetic function. One subject in the control groups, an 82-year-old lady had an abnormal deep breathing response and was unable to perform the valsalva manoeuvre.

In the scoring system devised for cardiac autonomic neuropathy, a normal response scored 0, a borderline response scored one and an abnormal response scored two. The total score for the three tests of cardiac function (deep breathing, valsalva, and change in heart rate on standing) was then calculated. A total score of zero or one was designated as representing no cardiac autonomic neuropathy. A total score of two or three represented mild involvement, and a total score of four to six indicated severe cardic autonomic neuropathy.

On this basis three of the 11 patients had mild and one patient had severe cardiac autonomic neuropathy (Table III). In the control group, ten subjects had no evidence of cardiac autonomic neuropathy, and one subject (aged

Table II *Tests of cardiovascular autonomic function (Ewing and Clarke).*

	Normal	Borderline	Abnormal
Parasympathetic Function:			
Heart Rate Response to Deep Breathing	$\geqslant$ 15 Beats/Min	11–14 Beats/Min	$\leqslant$ 10 Beats/Min
Heart Rate Response to Valsalva	$\geqslant$ 1.21	1.11–1.20	$\leqslant$ 1.10
Heart Rate Response to Standing (30/15 Ratio)	$\geqslant$ 1.04	1.01–1.03	$\leqslant$ 1.00
Sympathetic Function:			
Systolic Blood Pressure Response to Standing	$\leqslant$ 10mm Hg	11–29mm Hg	$\geqslant$ 30mm Hg

Table III *The measurement of parasymathetic autonomic function in eleven Holmes Adie Patients*

Patient	Sex	Age Years	Duration	Bilateral	Deep Breathing beats/min	Valsalva Ratio	Standing 130/15 ratio	Resting Heart Rate beats/min	Coefficient of Variation	Cardiac Autonomic Score
1	F	50	6 Months	No	21.5	1.50	1.09	92.0±0.2	3.8	0
2	F	54	20 Years	No	16.0	1.73	1.31	62.4±0.1	4.1	0
3	F	45	2 Months	No	20.0	1.85	1.16	87.0±0.2	6.1	0
4	F	58	20 Years	No	18.5	1.47	1.08	70.4±0.1	3.3	0
5	F	83	30 Years	Yes	5.2[1]	—	0.03[1]	79.7±0.1	2.3	2
6	M	30	1 Year	No	19.7	1.65	1.72	57.7±0.1	7.1	0
7	F	66	3 Months	No	2.2[2]	1.21	1.04	63.5±0.1	2.8	2
8	F	47	6 Months	No	7.3[2]	Abnormal[3]	1.16	80.4±0.4	4.0	4
9	F	49	2 Months	Yes	8.2[2]	1.45	1.04	91.3±0.2	4.1	2
10	M	40	9 Months	No	28.7	1.73	1.37	74.7±0.1	3.2	0
11	M	39	4 Months	No	18.3	1.91	1.32	70.2±0.1	4.7	0

[1] Denotes borderline response.
[2] Denotes abnormal response.
[3] Patient 8 showed no increase in heart rate during the strain period of the Valsava, instead there was a marked bradycardia throughout.

82), had mild cardiac autonomic neuropathy (Table IV). The average cardiac autonomic score for both groups is shown in Table V.

The results of the change in systolic blood pressure on standing, an index of sympathetic function, are shown in Table VI. The fall in systolic blood pressure on standing was in the borderline range in three of the 11 patients with Holmes Adie Syndrome. In the control group, the fall in systolic blood pressure on standing was in the borderline range in four subjects. The fall in systolic blood pressure was not frankly abnormal in either the group with Holmes Adie Syndrome or the control group. None of the subjects with a borderline response were symptomatic.

There was a wide variation in the resting heart rate of the different patients measured over a period of 512 beats. Resting heart rate variability over 512 beats was expressed in terms of the coefficient of variation. For the Holmes Adie patient, the mean value was 4.1. This was lower than in the group of 11 controls where the mean value was 6.5. Patients 5 and 7, in the Holmes Adie group had particularly low values.

When considered as a group, however, the Holmes Adie patients were not significantly different from the control group with respect to any of the autonomic responses studied.

There was no correlation between the known duration of the pupillary condition and the degree of cardiovascular autonomic impairment. Patient 5 had a 30 year history of Holmes Adie pupil but patients 7, 8 and 9 had histories of only three, six and two months

Table IV *The measurement of parasymathetic autonomic function in eleven age and sex matched controls*

Control	Sex	Age Years	Deep Breating beats/min	Valsalva Ratio	Standing 30/15 ratio	Resting Heart Rate beats/min	Coefficient of Variation	Cardiac Autonomic Score
1	F	53	20.0	1.40	1.20	77.0	4.4	0
2	F	56	15.0	1.55	1.07	72.0	3.1	0
3	F	45	22.8	1.85	1.28	66.9±0.2	7.0	0
4	F	62	36.0	1.80	1.35	62.0	12.6	0
5	F	82	2.3[1]	—	1.07	64.7±0.1	2.1	2
6	M	28	15.5	1.56	1.58	59.2±0.2	6.8	0
7	F	68	19.0	1.36	1.10	57.0	4.5	0
8	F	45	26.0	1.74	1.40	80.9±0.3	7.6	0
9	F	49	20.3	1.90	1.38	80.7±0.3	7.7	0
10	M	40	19.8	2.13	1.40	54.7±0.2	8.9	0
11	M	39	23.7	1.56	1.48	60.2±0.2	6.9	0

[1] Denotes abnormal response.

Table V *Number of patients with autonomic neuropathy, and mean cardiac autonomic score in patients with Holmes Adie Syndrome and Control Group*

Patient Group	Mean Cardiac Autonomic Score	Number of Patients No Neuropathy	Mild Neuropathy	Severe Neuropathy
Holmes Adie	0.91±0.41	7 (64%)	3 (27%)	1 (9%)
Controls	0.18±0.18	10 (91%)	1 (9%)	0 (0%)

respectively. On the other hand, patients 2 and 4 both had a 20 year history of Holmes Adie Syndrome, but showed no evidence of cardiovascular autonomic dysfunction.

Only two patients in the group had bilateral pupillary involvement and both (5 and 9) had mild autonomic dysfunction.

Discussion

Holmes Adie syndrome was originally described by Holmes in 1931.[1] He reported the association of pupillary abnormalities and loss of deep tendon reflexes. He used the term tonic pupil to describe the pupillary abnormalities, characterised by absent or partial loss of the light reflex, slow tonic sustained response on convergence. Adie in 1931 recognised incomplete forms of the disorder, where a tonic pupil occurred in the presence of normal reflexes.[2] These cases he considered to be milder forms of the same disorder. He described the syndrome as a benign condition, unassociated with other illnesses.

Tonic pupils can occur secondary to autonomic neuropathy. Throughout the literature, patients with Holmes Adie Syndrome are described as having no evidence of autonomic dysfunction elsewhere. Patients with Holmes Adie Syndrome are clearly differentiated from the group of patients with tonic pupils, occurring as part of a more generalised autonomic neuropathy.[9,10]

Ross's syndrome consists of segmental anhydrosis, tonic pupil and loss of deep tendon reflexes.[11] It has been differentiated from Holmes Adie syndrome.[9] However, in a recent study of a group of patients with Holmes Adie syndrome, sweating deficits were demonstrated in 11 of 53 patients.[12]

We used a standard battery of tests, as described by Ewing and Clarke, to assess autonomic function by the measurement of cardiovascular reflexes.[7] Current evidence suggests that this assessment of cardiovascular reflexes reflects damage elsewhere in the autonomic nervous system.[13]. The tests used detect both clinical and subclinical autonomic system damage.

Parasympathetic function was assessed by the measurement of heart rate response to deep breathing, valsalva manoeuvre and standing. Heart rate variability, an index of both sympathetic and parasympathetic function was also measured. Sympathetic function was assessed by the measurement of the fall in systolic blood pressure on standing.

Table VI *Measurement of sympathetic function: blood pressure. Change on standing in patients with Holmes Adie Syndrome and Control Group*

Patients with Holmes Adie Syndrome	Systolic Blood Pressure Change on Standing mm Hg	Control Group	Systolic Pressure Change on Standing mm Hg
1	−4.0	1	−10.0
2	+10.0	2	−8.0
3	−3.0	3	−4.0
4	−1.0	4	−12.0*
5	−28.0*	5	−18.0*
6	+2.0	6	−6.0
7	−12.0*	7	−15.0*
8	+2.0	8	−4.0
9	−26.0*	9	−5.0
10	+7.0	10	−2.0
11	+2.0	11	−16.0*

*Denotes borderline response

Normal, borderline and abnormal responses for the heart rate response to deep breathing, valsalva manoeuvre and standing, the change in systolic blood pressure on standing, were those defined by Ewing and Clarke.[7] The heart rate variability is not part of the standard battery of tests described by Ewing and Clarke. Loss of normal heart rate variability at rest was first described as a manifestation of autonomic neuropathy by Wheeler and Watkins.[14]

Four of 11 patients with Holmes Adie syndrome demonstrated abnormalities of parasympathetic function. All four had abnormalities as detected by the heart rate response to deep breathing, valsalva manoeuvre and standing. Only one of the 11 controls demonstrated abnormalities of parasympathetic function.

Autonomic function is known to decline with age.[15,16] One of the patients with Holmes Adie Syndrome (patient 5) was 83 years of age, and had mild impairment of autonomic function. An 82-year-old female healthy subject, in the control group also had mild impairment of autonomic function. Therefore, the presence of mild impairment of autonomic function in patient 5 may be an age related finding.

Heart rate variability overall was lower in the Holmes Adie group than the control group. This is a further indication of autonomic impairment.

Of the group with Holmes Adie, three developed a borderline fall in systolic blood pressure on standing. In the control group, four subjects developed a borderline fall in systolic pressure on standing. None of the responses were in the abnormal category. This test gives abnormal results only in the presence of severe peripheral sympathetic damage.

There appeared to be no relationship between the occurrence of cardiovascular abnormalities and the duration of the pupillary condition. Only two of the patients studied had bilateral pupillary involvement and both had disturbances of cardiovascular autonomic function.

The incidence of parasympathetic autonomic neuropathy as determined by assessment of cardiovascular reflexes was greater in 11 patients with Holmes Adie syndrome, than in an age and sex matched group of controls.

To our knowledge, abnormalities of cardiovascular reflexes have not previously been documented in patients with Holmes Adie Syndrome. Our initial findings suggest that autonomic dysfunction may be more widespread in these patients than was previously suspected and further study into this aspect of the syndrome is indicated.

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References

[1] Holmes G: Partial iridoplegia associated with symptoms of other diseases in the nervous system. *Trans. Ophthalmol. Soc. UK* 1931, **51:** 209–28.

[2] Adie WJ: Tonic pupils and absent tendon reflexes, a benign disorder sui generis: its complete and incomplete forms. *Brain* 1932, **55:** 98–113.

[3] Loewenfeld IE and Thompson HS: The tonic pupil: A re-evaluation. *Am. J. Ophthalmol.* 1967, **63:** 46–87.

[4] Harriman DGF and Garland H: The pathology of Adies Syndrome. *Brain* 1968, **91:** 401–18.

[5] Bourgon P, Pilley SFJ, Thompson HS: Cholinergic supersensitivity of the iris sphincter in Adies tonic pupil. *Am. J. Ophthalmol.* 1978, **85:** 373–7.

[6] Selhorst JB, Madge G, Ghatol NR, Richmond VA: The neuropathology of the Holmes Adie Syndrome. *Ann Neurol.* 1984, **16:** 138.

[7] Ewing DJ and Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br. Med. J.* 1982, **285:** 916–18.

[8] Mitchell RB, Sharief BS: Cahill SJ, Jenkins JG, McClure BG: Proceedings of the IEEE Montech 1987 Conference on Biomedical Technologies, Montreal 1987: 167–170.

[9] Thompson HS: Topics in Neurophthalmology. Baltimore, Williams & Wilkins Co. 1979: 95–113.

[10] Abbruzzese G, Abbruzzese M, Fauale E, Ratto S: Tonic vibration reflex in Holmes Adie Syndrome: An electrophysiological study. *J. Neurol, Neurosurg, Psychia* 1979, **42:** 943–47.

[11] Ross AT: Progressive sudomotor denervation. *Neurology* 1958, **8:** 809–17.

[12] Bacon PJ and Smith S: Adie's Syndrome: *Ophthalmic Dialogue* 1988 No. 3.

[13] Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. *Q. J. Med.* 1980, **49:** 95–108.

[14] Wheeler T and Watkins PJ: Cardiac denervation in diabetes. *Br. Med. J.* 1973, **4:** 584–6.

[15] Wieling W, Van Brederode JFM, De Rijk LG, Borst C and Dunning AJ: Reflex control of heart rate in normal subjects in relation to age: a database for cardiac vagal neuropathy. *Diabetologia* 1982, **22:** 163–66.

[16] Smith SA: Reduced sinus arrhythamia in diabetic autonomic neuropathy: diagnostic value of an age-related normal range. *Br. Med. J.* 1982, **285:** 1599–601.