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Autonomic Neuropathy in Leprosy[1]

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In autonomic neuropathy cardiovascular reflexes may be impaired. The integrity of the autonomic control of the heart can be studied by observing the heart rate during simple tests which can easily be performed at the bedside ([1,4,5,16]).

Leprosy is known to damage both somatic and autonomic nerves ([8,12]). However the effect of leprosy on the autonomic control of the cardiovascular system has not been described in detail.

The present study was initiated to assess the extent of autonomic impairment of cardiovascular reflexes in 21 patients with long-standing lepromatous leprosy regularly attending the Leprosy Clinic, Infectious Diseases Hospital, Athens, Greece.

MATERIALS AND METHODS

We studied 21 patients (8 men and 13 women) with leprosy, and 10 normal people (4 men and 6 women). The patients were drawn from the population attending the Leprosy Clinic, Infectious Diseases Hospital, Athens, and the control group consisted of healthy medical staff. The leprosy patients ranged in age from 39–81 (mean 55 years) and the control group from 28–62 (mean 47 years).

All 21 patients had the lepromatous type of leprosy with a characteristic early history of disseminated nodules and infiltrated plaques on the face, trunk and extremities. Eyebrow and eyelash loss, leonine facies and pendulous earlobes were noted in some cases. All 21 patients developed leprosy at least two years before chemotherapy was started. Thirteen of them remained without treatment for a period ranging from 5–17 years after the onset of symptoms. In some cases, therapy was discontinued intermittently because of poor patient compliance.

Criteria for inclusion in the study in the lepromatous patients were: a) the presence of leprosy for more than five years; b) the absence of lepra reactions during the study, and c) the ability to walk with no major malformations. Inclusion criteria for both groups were: d) no history of ischemic heart disease, normal resting ECG; e) the absence of other causes of autonomic neuropathy such as diabetes mellitus, amyloidosis, porphyria and syphilis as shown by relevant investigations; f) no drugs taken which were likely to affect autonomic nervous system function, and g) willingness to give informed consent.

Procedures

The subjects rested supine for at least 20 min before the investigation. Standard 12 lead electrocardiograms were performed and lead II strips recorded for measurement of heart rate.

The following non-invasive tests of autonomic cardiovascular control were performed:

Heart rate variability during deep breathing.

Response to mental stress, consisting of rapid performance of subtraction tests aloud under mild harassment.

Carotid sinus pressure. Firm pressure was applied for 15 sec each carotid sinus in turn.

Valsalva maneuver. Patients blew into a modified mercury sphygmomanometer. A pressure of 40 mm Hg was reached as soon as possible and maintained for 10

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sec. Pressure was then released abruptly and recordings were continued for at least another 20 sec.

Tilting. Patients were tilted to vertical for 3 min.

Between the above tests the patients rested in the supine position for 15 min. The pulse rate had returned to control levels before the next test. Statistical analysis was performed using Student's *t* test, White's Sum of Ranks, the non-parametric *t* test, and non-parametric rank correlation.

RESULTS

The results are illustrated in Tables 1, 2, and 3.

Heart rate variability. There were no significant changes in heart rate during deep breathing in the lepromatous patients. The mean minimum heart rate was 82.1 beats per minute and the maximum was 84.3. In contrast there were significant changes in the normal group ($p < 0.02$) with mean minimum heart rate of 83.0 and maximum of 104.4 beats per minute. The mean percentage heart rate change during deep breathing was 2.7 in the lepromatous patients and 26.0 in the control group ($p < 0.0001$).

Mental stress. Mental stress did not affect the heart rate significantly in either group. The mean heart rate was 70.7 beats per minute at rest and 70.2 after mental stress in the lepromatous patients, and 75.3 at rest and 87.4 after mental stress in the control group. However the mean percentage heart rate change was significantly higher in the control group ($p < 0.005$).

Carotid sinus pressure. There were no changes in heart rate with carotid sinus pressure in the lepromatous patients, but there were significant changes in the control group. In the lepromatous patients the mean resting heart rate was 67.3 beats per minute before pressure was applied to the right carotid artery, and 68.1 during right carotid pressure. The mean resting heart rate was 67.3 beats per minute before pressure was applied to the left carotid artery and 68.2 during left carotid pressure. In the control group the mean resting heart rate was 75.3 beats per minute before pressure was applied to the right carotid artery and 62.8 beats per minute during right carotid pres-

TABLE 1. *Heart rate (HR) in lepromatous leprosy patients and the control group, related to sex and various tests.*

	Leprosy patients																				Control group									
	Males								Females												Males					Females				
Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4	5	6	7	8	9	10
Mean resting HR	64	78	78	51	66	59	69	63	70	79	74	63	84	70	65	56	79	76	63	61	67	53	80	95	65	70	65	80	85	69	75
Difference between maximum & minimum HR during deep breathing	2	6	0	4	1	1	3	2	6	0	1	3	1	0	4	2	2	0	2	2	3	15	22	25	20	28	27	15	30	15	17
HR with mental stress	63	77	82	51	65	65	67	65	–	83	79	63	–	73	–	66	80	83	60	67	66	53	97	108	77	98	73	95	110	91	75
HR with pressure R carotid	62	77	70	48	67	68	67	58	71	82	67	63	93	67	66	54	75	86	61	59	68	41	60	85	55	65	50	60	68	65	52
HR with pressure L carotid	62	74	71	50	62	60	65	58	88	80	67	63	84	67	66	–	76	79	59	62	71	43	62	70	45	60	53	70	70	63	52
HR with Valsalva	74	78	99	52	72	68	69	66	69	80	73	66	96	77	69	57	77	70	59	70	83	53	74	88	52	63	59	66	73	58	70
HR with tilting at 15th beat	79	87	99	78	79	83	74	67	99	96	83	78	96	79	81	–	111	108	79	67	93	66	115	125	81	115	120	103	136	120	93
HR with tilting at 30th beat	85	72	99	98	80	83	84	65	98	72	76	96	99	84	76	–	72	105	98	75	73	60	83	107	73	85	73	81	125	100	76

TABLE 2. *Mean heart rates at rest and after test situations in leprosy patients and the control group.*

	Leprosy patients		Control group	
	Mean HR	Significance	Mean HR	Significance
Deep breathing max Deep breathing min	84.3 82.1	N.S.	104.4 83.0	$p < 0.02$
Rest Mental stress	70.7 70.0	N.S.	75.3 87.4	N.S.
Rest R carotid pressure	67.3 68.1	N.S.	75.8 62.8	$p < 0.05$
Rest L carotid pressure	67.3 68.2	N.S.	74.9 60.3	$p < 0.025$
Rest Valsalva maneuver	68.0 72.6	$p < 0.01$	72.2 65.4	N.S.
Rest Tilting at 15th beat	68.7 85.8	$p < 0.001$	75.5 107.4	$p < 0.005$
Rest Tilting at 30th beat	68.7 84.5	$p < 0.005$	75.5 86.30	N.S.

sure ($p < 0.05$). The mean resting heart rate was 74.9 beats per minute before pressure was applied to the left carotid artery and 60.3 beats per minute during left carotid pressure ($p < 0.025$). The mean percent heart rate changes during carotid pressure were significantly greater ($p < 0.0001$) for the control group than for the lepromatous patients.

Valsalva maneuver. In the lepromatous patients the mean heart rate changed from 68.0 beats per minute at rest to 72.6 beats per minute with the Valsalva maneuver ($p < 0.01$). Only three patients showed reflex bradycardia. All the people in the control group showed reflex bradycardia except for one in whom the heart rate did not change. The mean heart rate in this group changed from 72.2 beats per minute at rest to 65.4 beats per minute with the Valsalva maneuver.

Tilting. All patients responded to standing with a significant tachycardia at about 10 seconds which persisted in most cases until after 20–30 seconds. The mean resting heart rate was 68.7 beats per minute and increased to 85.8 beats per minute after tilting ($p < 0.001$). The mean 30:15 beat ratio (length of R-R interval at beat 30 divided by length of R-R interval at beat 15) ([1]) was 1.01. In the control group the mean resting heart rate was 75.5 beats per minute and increased to 107.4 beats per minute after tilting ($p < 0.005$), and the 30:15 beat ratio was 1.24. This was significantly different ($p < 0.0005$) from that of the patient group.

DISCUSSION

The results indicate that these patients with long-standing lepromatous leprosy have defective autonomic control of the heart. Impairment of vagal function was

TABLE 3. *Mean percent heart rate changes from rest and after test situations in leprosy patients and the control group.*

	Leprosy patients	Control group	Significance
%Δ HR min/max (deep breathing)	2.70	26.07	<0.0001
%Δ HR rest/mental stress	−0.16	16.32	<0.0005
%Δ HR rest/R carotid pressure	1.07	21.80	<0.0001
%Δ HR rest/L carotid pressure	0.02	25.89	<0.0001
%Δ HR rest/Valsalva maneuver	7.28	10.76	N.S.
%Δ HR rest/tilting (15th beat)	25.52	44.25	<0.01
%Δ HR rest/tilting (30th beat)	23.28	16.16	N.S.
%Δ R-R interval 30th/15th beat (tilting)	1.01	1.24	<0.0005

easily demonstrated by the different tests. Sympathetic impairment was less consistently demonstrated.

The variation in heart rate (sinus arrhythmia) which depends on the vagal innervation of the heart ([7,16,17]) was abolished. There was no significant difference in the lepromatous patients between the maximum and minimum heart rate during deep breathing (Table 2). In contrast the control group showed a significant difference in this parameter ($p < 0.02$) and the mean percent heart rate changes occurring from rest to after deep breathing were significantly different for the two groups ($p < 0.0001$). This test is probably the most sensitive for assessment of vagal function ([2,15]).

Mental stress causes tachycardia which is mediated by sympathetic mechanisms ([1,10,11]). In the present study there were no significant changes in heart rate in both groups after significant stress was applied. In the lepromatous patients the mean heart rate at rest was 70.7 beats per minute and after mental arithmetic under mild harassment was still 70 beats per minute. In the normal group the mean resting heart rate was 75.3 beats per minute, and after the same mental stress was 87.4 beats per minute. The mean percent heart rate changes from rest to after mental stress in these two groups were statistically significant ($p < 0.0005$) indicating greater changes in the control group and probably impairment of sympathetic function in the lepromatous group.

The response to carotid sinus pressure, although sometimes erratic ([3]), is a useful test of vagal function. Carotid sinus pressure slows the pulse by six or more beats per minute, in over 50% of normal people, particularly in the elderly ([14]). In the patients with lepromatous leprosy there was no change in heart rate with carotid sinus pressure on either side. In the control group the carotid sinus pressure on either side produced significant bradycardia. These findings indicate defective vagal function in the lepromatous patients.

Valsalva rate responses are particularly useful in assessment of autonomic nervous function ([5]). The early strain bradycardia which is the normal response ([7]) and is usually 10% lower than the resting heart rate ([13]) did not occur in our patients with lepromatous leprosy who had statistically significant tachycardia (Table 2). In contrast the control group presented with early bradycardia with heart rates 9% lower than the resting heart rate (Table 2). These findings indicate vagal impairment in the lepromatous patients ([6,9]).

The lepromatous patients also showed a statistically significant increase in heart rate immediately after standing which, unlike that in normals ([1,4]), persisted for quite a long time. Ewing, *et al.* ([4]) showed that in people with normal autonomic control there is a rapid increase in heart rate with the first few beats after standing, followed by a plateau for a further 5–10 beats, and then a relative bradycardia which is maximal at about the 30th beat. The same investigators showed that the heart rate in diabetics with autonomic neuropathy increases slowly and continuously over the 30 beat period. Their drug studies showed that this response is mediated through the vagus. They found that the 30:15 beat ratio gives a simple numerical value that reflects the presence or absence of the relative bradycardia. Their patients with a 30:15 beat ratio of 1.00 or less had vagal damage. In patients with normal autonomic function the 30:15 beat ratio was 1.03 or more. Our patients with lepromatous leprosy had a 30:15 beat ratio of 1.01 and our control group a 30:15 beat ratio of 1.24. These findings also indicate vagal impairment in the lepromatous patients.

SUMMARY

The integrity of the autonomic control of the cardiovascular system was studied in 21 patients with lepromatous leprosy and in ten normal people using several simple tests based on cardiovascular reflexes.

Impairment of both parasympathetic and sympathetic function was demonstrated in the lepromatous patients.

RESUMEN

Se estudió la integridad del control autonómico del sistema cardiovascular en 21 pacientes con lepra lepromatosa y en 10 personas sanas usando pruebas simples basadas en los reflejos cardiovasculares.

Se demostró una alteración en las funciones simpática y parasimpática en los pacientes lepromatosos.

RÉSUMÉ

On a eu recours à plusieurs épreuves simples, basées sur les réflexes cardio-vasculaires, pour étudier, l'intégrité du contrôle autonomique du système cardio-vasculaire chez 21 malades atteints de lèpre lépromateuse et chez 10 personnes normales.

On a pu démontrer que les fonctions parasympatiques étaient toutes deux endommagées chez les malades lépromateux.

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