

## SHORT REPORT

## High blood pressure and decreased heart rate variability in the Cuban epidemic neuropathy

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Autonomic cardiovascular reflexes were investigated in patients with an epidemic optic and peripheral neuropathy, which affected more than 50 000 people in Cuba between 1991 and 1994 and was probably caused by nutritional deficiency. Affected patients had significantly higher blood pressure than age matched controls, both while supine and standing, and significantly lower heart rate variability during paced breathing, suggesting reduced cardiac parasympathetic innervation.

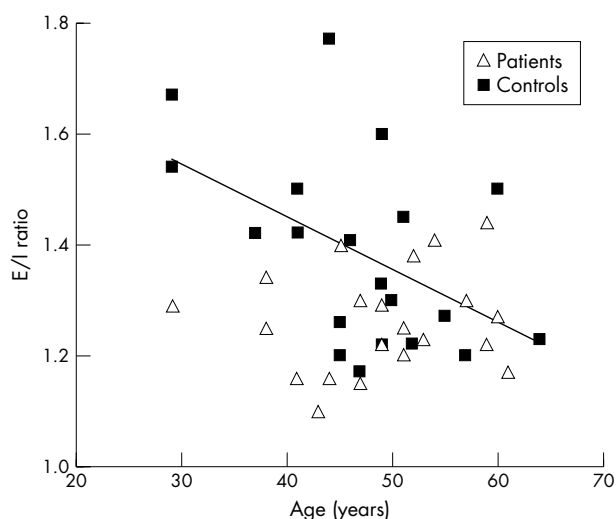
Between 1991 and 1994, an epidemic optic and peripheral neuropathy affected more than 50 000 people in Cuba among a population of 10.8 million.<sup>1,2</sup> The neuropathy coincided with a period of dramatic worsening of the island's economic situation and has been linked to deficiency of nutrients, including methionine, vitamin B-12, riboflavin, and carotenoids, because widespread distribution of vitamin supplements, which began in April 1993, effectively halted the occurrence of new cases.<sup>3</sup> A strong association with cigar smoking and increased cassava consumption, both of which contain cyanide, has also been found.<sup>3</sup>

Affected patients presented with retrobulbar optic neuropathy and a predominantly sensory peripheral neuropathy.<sup>4</sup> Most patients also had diarrhoea, palpitations, and genitourinary disorders of varying severity suggesting involvement of autonomic fibres.<sup>5</sup> Autonomic involvement was also suggested by low amplitude sympathetic skin responses.<sup>5</sup> To determine whether the neuropathy produced long lasting effects on autonomic function, we investigated autonomic cardiovascular reflexes in patients who had been severely affected during the epidemic.

## METHODS

We studied 21 patients (six men, 15 women; mean (SD) age 49 (8) years) with severe to moderate epidemic optic and peripheral neuropathy, based on published criteria,<sup>3,6</sup> including loss of fibres in the papillomacular bundle as assessed by a neurophthalmologist (RS) on fundoscopic examination on dilated eyes. Average duration of the disease was 7.3 years. Patients' results were compared with those of 21 age matched normal controls (three men, 18 women; mean (SD) age 47 (9) years) of similar ethnogeographic background. A complete neurological examination and autonomic testing was performed in a quiet room in the morning at the Instituto de Neurología y Neurocirugía, Havana, Cuba and in a mobile autonomic unit in the province of Pinar del Rio, the most affected area during the epidemic.

Electrocardiograms and blood pressure waveforms were recorded continuously with a Colin Pilot 9200 Unit (Colin Medical Instruments Corporation, San Antonio, Texas, USA). Analogue signals were digitised online at 333 Hz per channel using DI-720P data acquisition interface (DATAQ Instruments, Akron, Ohio, USA) and stored on a computer for later



**Figure 1** Expiratory/inspiratory (E/I) ratio v age in 21 patients with the Cuban epidemic neuropathy and 21 controls. The regression line represents significant negative correlation observed in controls ( $r = -0.50$ ,  $p < 0.05$ ), but not in patients.

analysis with custom written software. Patients were studied supine and while standing motionless for three minutes. Supine recordings were performed during five minutes of spontaneous breathing, during deep breathing at six cycles per minute for one minute, and during a standardised Valsalva manoeuvre. The expiratory/inspiratory ratio (E/I) was calculated by dividing the longest R-R intervals during expiration by the shortest R-R intervals during inspiration while the subjects were breathing at a rate of six breaths a minute (10 second cycle: five seconds of inspiration). The Valsalva ratio was derived as the ratio of the longest R-R interval during phase IV to the shortest R-R interval during phase II of the Valsalva manoeuvre.

Data are presented as mean (SD). Measures of autonomic function in patients and controls were compared using independent measures *t* tests. Blood pressure and heart rate data while supine and during active standing were analysed using two way repeated measures analysis of variance, followed, if significant, by multiple comparison tests with Bonferroni correction. All analyses were performed using the SPSS statistical package for Windows, version 9.0.  $p < 0.05$  was considered significant.

## RESULTS

At the time of the investigation, no patient had facial weakness or other cranial nerve deficits. Limb weakness was a complaint in 86% of the patients. Decreased muscle strength was documented clinically in the legs in 43% of patients, and in the arms in 24%. Ankle reflexes were decreased in 33% of patients. Sensory abnormalities were present in all patients:

negative sensory symptoms and signs (hypoalgesia, analgesia, thermal sensation) in 90% and positive sensory symptoms and signs (paresthesia and hyperalgesia) in 100%.

In the supine position, both systolic and diastolic blood pressures were significantly higher in patients (134 (20)/77 (10) mm Hg, systolic/diastolic) than in controls (118 (15)/67 (9) mm Hg,  $p < 0.05$ ). Heart rates were similar in patients (70 (10) beats/min) and controls (70 (9) beats/min). During active standing, only systolic blood pressure remained significantly higher in patients (134 (21)/79 (13) v 120 (18)/74 (13) mm Hg after one minute standing, and 135 (18)/76 (16) v 121 (18)/74 (13) mm Hg after three minutes standing ( $p < 0.05$ ). Orthostatic heart rate changes were similar in patients and controls (80 (11) v 81 (10) beats/min and 78 (11) v 78 (11) beats/min after one and three minutes standing).

The E/I ratio was significantly lower in patients (1.26 (0.09)) than in controls (1.38 (0.17)) ( $p < 0.01$ ). The expected negative correlation between E/I ratio and age was significant in controls (Pearson correlation,  $r = -0.50$ ,  $p < 0.05$ ) but not in patients (fig 1). The Valsalva ratio (1.52 (0.32) v 1.56 (0.32)) was lower in patients than controls, but the difference was short of significance.

## DISCUSSION

We found that patients with the Cuban epidemic neuropathy had higher blood pressure and decreased heart rate variability. Decreased heart rate variability indicates reduced parasympathetic outflow to the heart, a characteristic abnormality in patients with autonomic neuropathies. Sural nerve biopsies in patients with the Cuban epidemic neuropathy showed axonal damage in large diameter myelinated nerve fibres.<sup>7</sup> Our findings of impaired parasympathetic cardiac modulation suggest neurophysiological involvement of small nerve fibres as well. This is supported by previous findings of impaired thermal thresholds in these patients.<sup>3</sup> Decreased heart rate variability has also been reported in patients with vitamin B-12 deficiency,<sup>8,9</sup> but the defect was corrected by vitamin B-12 replacement therapy. In contrast, in patients with the Cuban epidemic neuropathy, decreased heart rate variability persisted, despite treatment with vitamin supplements for several years, suggesting permanent sequelae, similar to that observed in the somatic nervous system.

The cause of the higher blood pressure in these patients is not apparent. A history of high blood pressure was observed in 29% of patients with Cuban epidemic neuropathy and in 29% of normal controls ( $p = 0.95$ ,  $\chi^2$  test), suggesting that it was not due to hereditary factors. Blood pressure elevations, particularly in supine patients, occur with dysautonomia.<sup>10,11</sup> Interestingly, nutritional deficiencies and lower folate intake, as had occurred in the affected Cuban patients, have been associated with higher blood pressure in urban African-American and Hispanic adolescents in the United States.<sup>12</sup> Also, because arterial hypertension has been associated with decreased

heart rate variability, we cannot exclude the possibility that the higher blood pressure in our patients contributed to reduced parasympathetic activity to the heart.<sup>13</sup>

A similar neuropathy outbreak in which nutritional deficiency was implicated has been reported in Tanzania.<sup>14</sup> Affected patients also showed features suggestive of autonomic involvement, indicating that nutritional deficiencies probably affect nerve fibres of both large and small diameter and may leave permanent sequelae.

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