Original article

Cardiovascular autonomic neuropathy in HIV infected patients

Karen E Rogstad, Reena Shah, G Tesfaladet, Mohammed Abdullah, Imtyaz Ahmed-Jushuf

Objective: To evaluate the presence and extent of autonomic dysfunction in HIV infected individuals of one ethnic group.
Design: Prospective, age-sex matched study.
Methods: 25 patients (seven asymptomatic (HIV), eight AIDS related complex (ARC), 10 AIDS) and 25 controls were recruited from patients and staff at the Aga Khan Hospital, Nairobi. Autonomic function was assessed by measurement of pulse rate variability on standing, rest, deep breathing, Valsalva manoeuvre, isometric exercise, cold face test, and mental stress. Blood pressure was measured during standing, supine resting, and on Valsalva manoeuvre. CD4 count was correlated with number of abnormal test results.
Results: 21 patients had at least one abnormal test of autonomic function compared with one control ($p<0.0001$). There were significant differences between AIDS patients and controls for supine heart rate ($p<0.001$), Valsalva ratio ($p=0.05$), and cold face test ($p=0.05$), and almost significant results for mental stress ($p=0.051$). Evidence of autonomic hypersensitivity was found in response to exercise and/or mental stress in some patients with HIV or ARC. No difference was found in blood pressure measurements. Abnormalities in autonomic function occurred at all CD4 counts and all patients with four abnormal tests of heart rate variation had a CD4 count less than 300×10^6/l.
Conclusions: There is evidence of substantial autonomic dysfunction in AIDS patients compared with controls and mild abnormalities in the majority of HIV infected patients studied irrespective of CD4 count. Autonomic hypersensitivity may precede loss of function in some cases.
(*Sex Transm Inf* 1999;**75**:264–267)

Keywords: autonomic neuropathy; HIV; AIDS; Africa

Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield
K E Rogstad

University of Southampton Medical School
R Shah

Aga Khan Hospital, Nairobi
G Tesfaladet
M Abdullah

Department of Genitourinary Medicine, City Hospital, Nottingham
I Ahmed-Jushuf

Correspondence to:
Dr K E Rogstad, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

Accepted for publication
24 May 1999

Introduction

Abnormalities of the autonomic nervous system in HIV infection were first brought to our attention by Craddock *et al*,[1] who described syncopal reactions in four out of five AIDS patients (one of whom died), as a result of fine needle aspirations of the lung. These were reminiscent of typical vasovagal reactions, and the cardiorespiratory arrests following invasive procedures such as general and epidural anaesthesia,[2] which are a recognised complication of diabetic autonomic neuropathy. Autonomic tests on five patients showed abnormalities in at least two out of the three heart rate tests[1] suggesting that HIV infection may be associated with an autonomic neuropathy, exposing patients to risk following invasive procedures.

Despite the possible significance of these findings, and the suggestion by others of autonomic dysfunction in HIV infection,[3–6] little research has been undertaken on this topic. The studies which have been done to date have concentrated on HIV individuals who are homosexual, injecting drug users, or haemophiliacs. They have not been age and sex matched, nor have they controlled for ethnicity of patients, despite the fact that there appear to be significant differences in autonomic function between ethnic groups.[7] No study of which we are aware has been performed on those who predominantly acquired HIV through heterosexual transmission, or specifically on non-white people.

The aim of this study, therefore, was to evaluate the presence and extent of autonomic dysfunction in African HIV seropositive patients, compared with age and sex matched seronegative controls, and to correlate the dysfunction with stage of HIV infection.

Subjects and methods

SUBJECTS

Twenty five adult patients (13 male and 12 female) were recruited from a population of HIV infected patients who attended the Aga Khan Hospital, Nairobi, Kenya, between August 1994 and December 1994. Age and sex matched controls were recruited from outpatient clinics or were medical staff at the hospital. For HIV positive patients that were recruited from the wards, we recruited the appropriate seronegative controls from the wards. All ward patients and controls were recruited immediately before discharge. All patients and controls were of native African origin but were not from a single tribe. Testing for HIV antibody 1 and 2 had been performed on each patient using enzyme linked immunosorbent assay (ELISA) and confirmed by western blot at the laboratory of the Aga Khan Hospital. All controls had been confirmed HIV antibody negative by ELISA within the preceding year.

All patients and controls were afebrile and did not appear clinically dehydrated. None of the subjects was malnourished as assessed by body mass index (BMI). Autonomic function tests were not carried out on any patient or control who was acutely ill. Any subject being treated for, or with, tuberculosis or diabetes mellitus, alcoholism, multiple system atrophy, and other disorders known to affect the autonomic nervous system, were excluded. It was not possible to undertake routine chest *x* rays or fasting blood glucose/glucose tolerance tests on patients and controls nor to perform TB smear/culture, for the purpose of the study. No patient or control had taken zidovudine, zalcitibine, didanosine, or vincristine, and none of the subjects was taking antihypertensive or antidepressant therapy (which may interfere with autonomic responses). Full blood count, urea, creatinine, and electrolyte levels were checked on each patient to exclude anaemia, dehydration, and adrenal insufficiency and CD4 and CD8 cell counts were performed. Of the 25 HIV positive patients, one acquired HIV infection via a blood transfusion and 24 through heterosexual intercourse. Seven patients had asymptomatic HIV infection, eight had AIDS related complex (ARC) and 10 had AIDS.

Methods

Detailed clinical histories were taken from each patient and a review of their case notes performed.

Clinical examination of the nervous system was performed by one investigator.

Ethical approval was obtained both in Kenya and in England. Informed consent was obtained from the patients and controls after appropriate explanation of the testing procedure. An interpreter was available for those who did not speak English.

AUTONOMIC FUNCTION TESTING

On the day of testing, patients and controls were instructed not to ingest tobacco or caffeine containing products. Blood pressure was measured non-invasively using a Digital Electronic BP monitor Model DS-105E and heart rate was measured using an electrocardiograph machine (Logos 8821 EKG). The time interval between two successive R waves was measured manually using a "R-R Ruler" which translated the distance into heart rate. All subjects were given sufficient time to reach baseline values before autonomic tests were performed. The methods used were similar to those used for assessing diabetic autonomic neuropathy by Ewing and Clarke[8] and Bennett *et al* [9] and comprised:

- *R-R interval variability during quiet standing:* The mean heart rate was calculated as the average of the longest and shortest R-R interval.
- *R-R interval variability during supine rest:* The above measurements were repeated with the patient supine. These were used as resting heart rate values.
- *Heart rate variation with a single deep breath:* The seated subject was asked to inhale deeply and hold for 10 seconds. Heart rate was recorded 2 minutes before, during, and 2 minutes after the exercise. The longest R-R interval during, and the shortest R-R interval after, inhalation was determined. The heart rate at exhalation divided by the heart rate at inspiration (the E:I ratio) was calculated. The difference in heart rate between the slowest heart rate at inspiration divided by the fastest after, was also calculated.
- *Valsalva manoeuvre:* The seated subject was asked to exhale for 15–20 seconds against a resistance of 40 mm Hg in an open loop system. The blood pressure during and immediately after the Valsalva manoeuvre was measured. Patients were carefully observed to ensure that spurious Valsalva manoeuvres were not performed. The Valsalva ratio, the ratio of the maximum heart rate during the expiratory phase to the minimum heart rate during the relaxation phase (within 20 beats), was calculated. The difference between the maximum heart rate during the Valsalva manoeuvre and the minimum after the Valsalva manoeuvre was also calculated.
- *Isometric exercise:* The subject was instructed to squeeze a handgrip dynamometer for 3 minutes. The shortest R-R interval during the exercise and the longest R-R interval while relaxed (within five beats) was determined.
- *Cold face test:* Ice cubes were placed in a polythene bag and placed on the subject's forehead for 3 minutes. The longest R-R interval during the cold stimulus and the shortest before, was measured.
- *Assessment of response to mental stress:* The shortest R-R interval and the longest (within 5 beats) after the stress, was calculated.
- *Blood pressure variability:* The blood pressure was recorded. The differences in systolic and diastolic pressure between standing and lying were calculated.

STATISTICAL ANALYSIS

Initial comparisons of test results across all four diagnostic groups (controls, asymptomatic HIV, ARC, AIDS), were examined by one way analysis of variance; significant difference across these groups are indicated by χ^2. Variables were considered to be significantly different if $p \leq 0.05$.

Results

Twenty five HIV infected individuals and 25 HIV negative controls were assessed. The mean age of patients was 38 years (range 26–58 years) and of controls was 38.12 years (range 26–60 years). Of the 25 patients, 10 had a CD4 count less that 200×10^6/l.

On tests of heart rate variation, four patients (one asymptomatic, one ARC, two AIDS) had abnormal responses to four tests, two patients to three tests (one asymptomatic, one AIDS), six to two tests (one asymptomatic, four ARC, one AIDS), and nine to one test (four asymptomatic, two ARC, three AIDS). Only four patients (one ARC, three AIDS) had normal results. One control (number 21) had an

abnormal Valsalva ratio. Patients were significantly more likely to have at least one abnormal result compared with controls ($p<0.0001$). There were significant differences between AIDS patients and controls for supine heart rate ($p<0.001$), Valsalva ratio ($p = 0.05$), heart rate changes with cold face test ($p = 0.05$), and almost significant for mental stress ($p = 0.051$). For difference in heart rate on deep breathing there was a trend for worsening autonomic function from asymptomatic disease to AIDS, although this did not reach statistical significance.

Some patients with HIV and ARC had an exaggerated autonomic response on exercise suggesting autonomic hypersensitivity.

There were no significant blood pressure changes between standing and lying or on the Valsalva manoeuvre, although there was a trend for a higher change in blood pressure in patients compared with controls, possibly due to autonomic hypersensitivity. Abnormal tests of heart rate variation occurred at all levels of CD4 count but all patients with four or more abnormal results had a CD4 count of $<300 \times 10^6$/l.

Of the eight patients with the highest abnormal autonomic test scores, only two had clinical evidence of peripheral or central nervous system involvement.

Discussion

This study adds to the accumulating evidence that HIV affects autonomic nerves and this may explain some of the clinical features of AIDS. Exclusion criteria were strict. Patients with tuberculosis were ineligible as it may cause adrenalitis, and medications used for its treatment can lower blood pressure and cortisol levels (rifampicin) or cause polyneuritis (isoniazid). No patients were underweight, therefore malnutrition could not be a cause of their dysautonomia. Also on questionnaire analysis, fewer of the patients drank alcohol compared with controls ($p=0.02$) (unpublished data) thus excluding alcohol as a contributing factor.

Although the numbers were small, we have demonstrated significant abnormalities in autonomic function between controls and patients, using basic cardiovascular reflex tests which have well been validated.[8 9] Newer techniques for measuring autonomic function are more sophisticated and include computer analysis of the data. This project was performed in a resource-poor country where access to specialised equipment, for measuring autonomic function and computer analysis of it, was not available. Although the abnormalities in autonomic function did not correlate with signs of HIV associated neurological disease in our study as assessed by clinical examination, nerve conduction studies were not performed.

Autonomic abnormalities were particularly apparent in the tests for heart rate variation (mediated by the vagal nerve), such as the expiratory:inspiratory ratio, the Valsalva ratio, and cold face and mental stress tests.

We found that patients with AIDS had a significantly higher heart rate compared with other groups, a feature commonly observed in diabetic patients with autonomic neuropathy which is thought to represent unopposed cardiac sympathetic activity.[10] This was in the absence of evidence of dehydration, cardiac failure, or anaemia to account for it. Although subclinical myocardial dysfunction or myocarditis has been observed in HIV infection[11] and could cause a resting tachycardia we cannot exclude this possibility, nor were synacthen tests carried out to exclude adrenal insufficiency, which is common in HIV infection.[12]

The most pronounced abnormalities were found in patients with AIDS, but across groups there was a trend towards increasing autonomic dysfunction, from asymptomatic HIV disease to AIDS, and individual test results show gross abnormalities in patients with asymptomatic HIV (n=1), ARC (n=3) and AIDS (n=4). This shows that dysfunction can occur at any stage of the disease.

Several patients in the HIV and ARC group showed exaggerated normal responses to exercise, and in the HIV group they showed similar exaggerated response to mental stress. It has been suggested that there may be a transient appearance of hyperactive autonomic responses occurring over weeks to months, in patients with autonomic degeneration. This phenomenon has been attributed to denervation supersensitivity, and the exaggerated, normal responses observed in several ARC and HIV patients may reflect this phenomenon.

No significant changes in blood pressure were observed in this study but immediate orthostatic changes in blood pressure were not assessed. If they had been they may well have been abnormal as a questionnaire found a significant proportion of the HIV patients felt dizzy on standing up compared with controls ($p=0.0006$) (unpublished data).

Previous clinical studies have shown both positive and negative results.[13–15] Freeman *et al*[13] demonstrated significant abnormalities in autonomic function between 22 controls and 26 HIV positive patients (18 AIDS, eight ARC), measured by multiple tests of the autonomic nervous system, including haemodynamic response to tilting and standing.

Scott *et al*[14] carried out sequential autonomic function tests on 22 patients (13 asymptomatic, seven persistent generalised lymphadenopathy, two Kaposi's sarcoma) but found evidence of autonomic abnormalities in only one subject who also had AIDS related dementia.

Villa *et al*[15] studied 10 male and five female drug addicts, 10 of whom were HIV positive. (CDC group II (one), group III (five), group IVa (four). They measured the R-R interval variation during deep breathing and found that two were abnormal (CDC group III), suggesting that autonomic neuropathy could be an early indicator of HIV related neurological involvement. A study on 40 male HIV positive homosexuals found evidence of autonomic dysfunction in 15, but 11 were recruited

because of clinical features of neurological involvement.[16]

All subjects in this study were native black Africans and it is essential to control for ethnicity as Meyer *et al*[7] showed variation in autonomic function between native black Africans and Africans of white origin, and ethnic differences were also found by Venter *et al*.[17]

The mechanism for development of autonomic dysfunction in HIV positive patients is not known. Histological evidence showing depletion of autonomic axons in small bowel mucosa is well documented[18–20] and changes are found at all stages of infection,[21] reinforcing the view that autonomic neuropathy may develop early in the course of the disease.

Autonomic dysfunction may provide an alternative explanation for symptoms commonly observed in HIV infected individuals such as bowel and bladder dysfunction, impotence, syncope, sweating disorder and dry mouth which occur in the absence of any known aetiology, but the optimal treatment is not known. The presence of HIV related neurological disorder has been suggested as an indicator for treatment with zidovudine[22]; therefore, it may be appropriate to initiate antiretroviral therapy in patients with autonomic symptoms although, unfortunately, patients in this study and their countrymen do not have access to HAART because of cost. In view of the risk of fatal cardiorespiratory arrest, simple tests such as the measurement of R-R interval variation could be useful in patients undergoing diagnostic invasive procedures, although it is unclear whether it would predict arrest. Further work needs to be done to determine the value of autonomic testing, and regimes for the prevention and treatment of this complication of HIV infection.

We would like to thank all the staff and patients of the Aga Khan Hospital who contributed to this study and Professor Terry Bennet, University of Nottingham, for his advice on investigation of autonomic dysfunction and his comments on the manuscripts.

Funding: None.

Conflict of interest: None.

Contributors: K E Rogstad had the idea for the study, designed it, performed the data analysis, and wrote the final draft of the paper; R Shah tested the patients, performed the data analysis, and wrote the final draft of the paper; G Tesfaladet designed the study, enrolled the patients, and assessed the draft paper; M Abdullah and I Ahmed-Jushuf designed the study and assessed the draft paper.

1 Craddock C, Pasvol G, Bull R, *et al.* Cardiorespiratory arrest and autonomic neurotherapy in AIDS. *Lancet* 1987;ii:16–18.
2 Page MMcB, Watkins PJ. Cardiorespiratory arrest in diabetic autonomic neuropathy. *Lancet* 1987;i:14–16.
3 Miller RF, Semple SJG. Autonomic neuropathy in AIDS (letter). *Lancet* 1987;ii:343–4.
4 Cohen J, Laudenslager M. Autonomic nervous system involvement in patients with HIV infection. *Neurology* 1989;**39**:1111–12.
5 Lin-Greenberg A, Taneja-Uppal N. Dyautonomia and infection with the HIV (letter). *Ann Intern Med* 1987;**106**:167.
6 Parisi A, Di Perri G, Strosselli M, *et al.* Testing for neurological involvement in HIV infection (letter). *Lancet* 1987;ii:1531.
7 Meyer EC, Sommers De K, Schoeman HS, *et al.* The effect of autonomic blockers on heart rate: a comparison between two ethnic groups. *Br J Clin Pharmac* 1990;**29**:254–6.
8 Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab* 1986;**15**:855–88.
9 Bennett T, Farquhar I K, Hosking D J, *et al.* Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. *Diabetes* 1987;**27**:1167–74.
10 Wheeler T, Watkins PJ. Cardiac denervation in diabetes. *BMJ* 1973;**4**:584–6.
11 Cohen IS, Anderson DW, Virmani R, *et al.* Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. *J Am Coll Cardiol* 1988;**11**:792–9.
12 Abbott M, Khoo SH, Hamner MR, *et al.* Prevalence of cortisol deficiency in late HIV disease. *J Infect* 1995;**31**:1–4.
13 Freeman R, Roberts MS, Friedman LS, *et al.* Autonomic function and HIV. *Neurology* 1990;**40**:575–80.
14 Scott G, Piaggesi A, Ewing DJ. Sequential autonomic function tests in HIV infection. *AIDS* 1990;**4**:1279–82.
15 Villa A, Foresti V, Confalonieri F. Autonomic neuropathy and HIV infection (letter). *Lancet* 1987;ii:915.
16 Shahmanesh M, Bradbeer CS, Edwards A, *et al.* Autonomic dysfunction inpatients with human immunodeficiency virus infection. *Int J STD AIDS* 1991;**2**:419–23.
17 Venter CP, Joubert PH, Strydom WJ. Ethnic differences in response to pharmacological denervation of the heart. *IRCS Med Sci* 1984;**12**:963–4.
18 Griffin GE, Miller ARO, Batman P, *et al.* Damage to jejunal intrinsic autonomic nerves in HIV patients. *AIDS* 1988;**2**:379–82.
19 Miller ARO, Griffin GE, Batman P, *et al.* Jejunal mucosal architecture and fat absorption in male homosexuals infected with HIV. *Q J Med* 1988;**69**:1009–19.
20 Batman PA, Miller ARO, Forster SM, *et al.* Jejunal enteropathy associated with HIV infection:Quantitative histology. *J Clin Path* 1989;**42**:275–81.
21 Batman PA, Miller ARO, Sedgwick PM, *et al.* Autonomic denervation in jejunal mucosa of homosexual men infected with HIV. *AIDS* 1991;**5**:1247–52.
22 Sidtis JJ, Gatsonis C, Price RW, *et al.* Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. AIDS Clinical Trials Group. *Ann Neurol* 1993;**33**:343–9.