Symptoms of Autonomic Dysfunction in Human Immunodefi ciency Virus

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This retrospective study evaluated the frequencies of symptoms associated with autonomic dysfunction in human immunodeficiency virus (HIV)-infected patients on stable combined antiretroviral therapy. Patients infected with HIV reported higher frequencies of dysautonomia symptoms compared with HIV-negative patients, particularly in the autonomic domains related to urinary, sleep, gastroparesis, secretomotor, pupillomotor, and male sexual dysfunction.

Keywords. autonomic dysfunction; dysautonomia; HIV.

Autonomic dysfunction (AD) is common in patients infected with human immunodeficiency virus (HIV) and can result in symptoms such as orthostatic intolerance, gastrointestinal abnormalities, and male sexual dysfunction, which substantially impacts quality of life [1]. Human immunodeficiency virus-infected individuals with symptomatic autonomic neuropathy have increased morbidity [2]. In the pre-highly active antiretroviral therapy (ART) era, AD in patients infected with HIV was associated with longer duration of infection, uncontrolled HIV viremia, and exposure to older antiretroviral medications [3]. Combined ART (cART) has decreased the morbidity and mortality associated with immunosuppression [1]. However, the impact of cART on the prevalence of AD and its associated symptoms is unclear. This study aimed to determine the prevalence of symptoms of AD in virologically suppressed HIV-infected patients on cART.

METHODS

Study Design and Population
This is a substudy of the Hawaii Aging with HIV Cardiovascular Study, a longitudinal study of the role of oxidative stress and inflammation in HIV-associated cardiovascular risk [4]. Human immunodeficiency virus-positive patients on stable cART >3 months without prior cardiovascular disease, arrhythmia, or diabetes were recruited. Patients with hepatitis C virus (HCV) infection confirmed by presence of HCV antibody, hospitalization within 14 days before study entry, and active drug and alcohol abuse were excluded. Height, weight, body mass index, blood pressure, waist-to-hip ratio, electrocardiogram, fasting lipids, and 2-hour glucose tolerance were measured. Self-reported current and past smoking status was obtained. A convenient sample of HIV-seronegative patients who were often partners or friends of enrolled HIV-infected patients were recruited as a comparison group. Signed consent for study participation was obtained, and institutional review board approval was obtained from the University of Hawaii.

Formal Assessment of Autonomic Symptoms
Symptoms of AD were obtained with the Autonomic Symptom Profile (ASP), a 169-item validated questionnaire of symptoms across 11 domains of autonomic function [5]. The 11 domains with examples of symptoms are as follows: Orthostatic intolerance (light-headedness/dizziness on standing); Secretomotor (abnormal sweating, inability to tolerate heat and mucosal secretory dysfunction such as dry eyes/mouth); Urinary (urinary frequency/urgency, incontinence, or urinary retention); Gastroparesis (bloating, nausea, and vomiting); Constipation; Autonomic index, blood pressure, waist-to-hip ratio, electrocardiogram, fasting lipids, and 2-hour glucose tolerance were measured. Self-reported current and past smoking status was obtained. A convenient sample of HIV-seronegative patients who were often partners or friends of enrolled HIV-infected patients were recruited as a comparison group. Signed consent for study participation was obtained, and institutional review board approval was obtained from the University of Hawaii.

Formal Assessment of Autonomic Function
Formal autonomic function was assessed using a battery of standardized tests that assessed 3 areas of autonomic function:

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cardiovagal, adrenergic, and sudomotor. Patients fasted more than 8 hours, avoided heavy exercise more than 1 day before testing, and did not ingest caffeine, nicotine, or medication that might affect the test results [6]. The autonomic test battery were transformed into the Composite Autonomic Scoring Scale (CASS), a functional scale different from the questionnaire-derived COMPASS [5]. The Composite Autonomic Scoring Scale quantitates autonomic function into a 10-point scale and can validate COMPASS findings. A score ≤3 indicates no or mild autonomic failure, 4–6 indicates moderate failure, and ≥7 indicates severe failure.

**Statistical Analysis**

The objective of this study was to compare the prevalence and characteristics of autonomic symptoms between HIV-positive and HIV-negative patients. Categorical variables, including symptom frequencies, were compared using the χ² test. Continuous variables are presented as medians along with interquartile range (Q₁, Q₃) and analyzed by Wilcoxon rank test. A 2-sided probability of P < .05 was used to determine significance. All statistical analyses were performed using JMP, version 10 (SAS Institute Inc., Cary, NC).

**RESULTS**

The HIV-positive group consisted of 45 males and 3 females. The HIV-negative group consisted of 19 males and 3 females. There were no significant differences in median age (Q₁, Q₃) (HIV positive: 42 years [37, 50] vs HIV negative: 39 years [33, 41]), body mass index (HIV-positive: 24.2 kg/m² [22.9, 27.8] vs HIV negative: 25.1 kg/m² [23, 27.8]), nor current and/or former tobacco use between HIV-positive and HIV-negative groups (HIV-positive: 9 [18.8%] vs HIV-negative: 3 [13.6%]). All HIV-positive patients had an undetectable HIV RNA viral load, with a median CD4 count (Q₁, Q₃) of 465.5 copies/mL (296, 624). There were no differences between HIV-positive and HIV-negative patients in median systolic (HIV-positive: 116.5 mm Hg [110, 132.5] vs HIV-negative: 110.0 mm Hg [100, 116.5]) and median diastolic blood pressures (HIV-positive: 76 mm Hg [71.8, 80.5] vs HIV-negative: 76 mm Hg [68, 78.5]), and median heart rate (HIV-positive: 67 beats per minute [bpm], [58, 76.8] vs HIV-negative: 68 bpm [60, 72]).

Symptoms of AD were present in 40% of HIV-positive compared with 9% of HIV-negative patients. The most common symptoms of AD reported by HIV-positive patients involved orthostatic intolerance, sleep problems; secretomotor issues such as abnormal sweating; pupillomotor problems such as light sensitivity and visual blurring; and male sexual dysfunction (Figure 1). The HIV-positive group demonstrated a significantly higher prevalence of patients experiencing symptoms of AD in 6 of the 11 domains compared with the HIV-negative group. The greatest difference was seen in male sexual dysfunction with 47% of HIV-positive patients experiencing symptoms, compared with 11% of the HIV-negative patients (P = .002). Gastroparesis symptoms occurred in 37.5% in HIV-positive compared with 9.1% in HIV-negative patients (P = .015). Secretomotor dysfunction was noted in 58% of the HIV-positive compared with 26% in HIV-negative patients (P = .016). Pupillomotor, urinary, and sleep dysfunction were all higher in HIV-positive compared with HIV-negative patients (all P values <.05). With all autonomic domain symptoms taken together, more HIV-positive patients (40%) had a COMPASS score ≥30, which is suggestive of clinically significant autonomic neuropathy compared with HIV-negative patients (9%; P = .010) (Figure 1).

Thirty-three HIV-positive patients underwent formal autonomic function testing. None of the HIV-negative patients had formal autonomic function testing. Among 33 HIV-positive patients, 27 (82%) had a CASS score above zero. Nineteen (58%) had evidence by CASS scores indicating mild autonomic neuropathy. Moderate autonomic neuropathy (ie, CASS = 4–6) was evident in 24% (8 of 33), but none had severe autonomic neuropathy (ie, CASS ≥7). A significant correlation was present between COMPASS and CASS (β = 4.892, standard error = 2.076, P = .025).

**DISCUSSION**

Our study found symptoms of AD prevalent in virologically suppressed HIV-positive patients on cART. The exact mechanism by which HIV modulates autonomic function is unknown [8]. It is hypothesized that HIV promotes a sympathetic imbalance, contributing to a virus-friendly Th1-biased immune environment [9]. Clinically, AD in HIV-positive patients is consistent as a spectrum of HIV-associated neuropathies [9, 10]. Pathologic studies involving the jejunal mucosa of HIV-positive patients demonstrates that damage to the autonomic nerve fibers occurs early in the course of HIV infection [11]. Using heart rate variability, Becker et al [12] demonstrated that cardiac AD gradually occurs with HIV disease progression.

Autonomic dysfunction in the era of cART appears to be mild [13]. Study participants demonstrated a median CASS score consistent with our previously reported findings [14]. Our study adds to the literature by highlighting symptoms of AD experienced by HIV-positive patients, and these symptoms can be elicited on routine visits. In the pre-cART era, severe AD was observed with debilitating postural hypotension, syncope, or cardiopulmonary arrest [15]. Syncope was not common in our study; however, orthostatic intolerance continues to be a prevalent along with a diverse range of symptoms involving the secretomotor, pupillomotor, gastrointestinal, and genitourinary systems.
Our study is strengthened by the exclusion of patients with diabetes mellitus, HCV infection, and drug/alcohol use, which are associated risk factors for autonomic neuropathy. The fewer comorbidities experienced by participants in our study may in part account for the lower median CASS score reported compared with those reported by Robinson-Papp [13]. Similar to the study by Robinson-Papp et al [13], the autonomic symptoms noted in our study were nonspecific in nature.

We recognize that our study has limitations. This is an observational study of a small, convenient sample of patients from a single clinic without formal autonomic testing in all participants. As a result of this sampling, a limitation is the small percentage of women. In addition, we excluded individuals with diabetes, HCV infection, and drug/alcohol use because these factors may confound the findings in autonomic neuropathy. This may limit the generalizability of our findings given the higher prevalence of diabetes, HCV infection, substance abuse, and alcoholism in the HIV-infected population. However, we wanted to determine the effects of HIV and its treatment on autonomic function. Although the study groups were similar, HIV-negative patients were not matched to study participants. Vitamin B12, folate, thyroid studies, and rapid plasma reagin were not performed on all patients. Other comorbidities such as renal impairment were not being taken into account, although the number of patients with significant metabolic and renal disease was small and unlikely to impact the study findings. Despite these limitations, our study did demonstrate significant symptoms of AD in a well characterized population of virologically suppressed HIV-positive patients.

**CONCLUSIONS**

Human immunodeficiency virus-positive patients on suppressive cART have a higher prevalence of dysautonomia symptoms compared with HIV-negative patients. Further studies are needed to explore the prevalence, pathophysiology, clinical implication, and impact on quality of life of AD in HIV-positive patients on cART.

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**References**


2. Robinson-Papp J, Sharma SK. Autonomic neuropathy in HIV is unrecognized and associated with medical morbidity. AIDS Patient Care STDS 2013; 27:539–43.