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Hypertriglyceridemia in combination antiretroviral-treated HIV-positive individuals: potential impact on HIV sensory polyneuropathy

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Abstract

Objective—In HIV populations that are aging due to improved longevity with combination antiretroviral therapy (CART), both hypertriglyceridemia (hTRG) and sensory neuropathy have become increasingly common. Sensory neuropathy is associated with substantial long-term disability and frequently requires management with analgesics. Elevated serum triglycerides (TRGs) are associated with an increased risk for sensory neuropathy in diabetes mellitus. However, the contribution of hTRG to sensory neuropathy in HIV has not been carefully evaluated.

Design—Prospective, comparative, single-center, cross-sectional cohort study.

Methods—Clinical correlates of sensory neuropathy were assessed in HIV-positive and HIV-negative participants. HIV-sensory neuropathy was defined as one or more clinical signs of reduced distal sensation or ankle reflexes; symptoms were distal leg and foot pain, paresthesias or numbness. TRG levels were assessed along with concomitant metabolic and other risk factors including glucose, lipids, age, height, current and nadir CD4, and past or current use of protease inhibitors, dideoxynucleoside antiretrovirals (d-drugs), and statins in univariable and multivariable logistic regression.

Results—Of 436 HIV patients (median age 52 years; 75% on CART), 27% had sensory neuropathy; 48% were symptomatic. TRG levels were significantly higher in HIV-positive than HIV-negative individuals (mean $\pm$ SD, 245 $\pm$ 242 versus 160 $\pm$ 97 mg/dl; $P < 0.001$). Among HIV-positive patients, those with TRG levels in the highest tertile (≥ 244 mg/dl) were more likely to have sensory neuropathy than those in the lowest tertile (reference, < 142 mg/dl) after adjusting for concurrent predictors (adjusted odds ratio 2.7, 95% confidence interval 1.4–5.5).

Conclusions—Elevated triglyceride levels increased the risk for HIV-sensory neuropathy in HIV-positive individuals independently of other known risk factors.

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Keywords

antiretroviral; HIV; sensory neuropathy; triglyceride

Introduction

HIV infection is commonly associated with sensory neuropathy, with prevalence rates as high as 55% [1] depending on cohort characteristics. Signs of HIV-sensory neuropathy include diminished distal vibratory sensation, reduction in sharp sensation, and reduced ankle reflexes. Symptoms often include bilateral loss of sensation, hyperalgesia, tingling, pain, or burning or numbness of the feet, which may decrease mobility and reduce quality of life [2]. In the pre-combination antiretroviral therapy (CART) era, prevalence of HIV-sensory neuropathy signs and symptoms increased with low CD4 cell counts and high plasma HIV viral loads [3]. CART has improved immune function, suppressed HIV replication and decreased the incidence, but not prevalence of HIV-sensory neuropathy [3–5]. This persistence suggests that causes including age, height [6], alcohol abuse, nadir CD4 cell count, medications including protease inhibitors and d-drugs may contribute to its pathogenesis. [1,5]. HIV-sensory neuropathy is frequently associated with metabolic abnormalities such as hyperglycemia and hyperlipidemia [7–10]. We extended these observations by studying the association between hyperlipidemia and HIV-sensory neuropathy in HIV-positive patients on CART.

Methods

Study design

In this cross-sectional study HIV-positive and HIV-negative individuals were recruited at the HIV Neuro-behavioral Research Center (HNRC) UC San Diego. The Institutional Review Boards approved all research. All individuals were evaluated by comprehensive neuromedical assessments, phlebotomy, and lumbar puncture.

Participants

Data from 436 HIV-positive and 55 HIV-negative individuals seen between January 2000 and December 2009 with blood collection and neuromedical examination were analyzed. Characterization of HIV infection was carried out according to previously published guidelines used in CHARTER studies [10]. Details of past and current antiretroviral usage were captured by combined interviewer-administered questionnaires. Data collected included usage dates, dose, and schedule for each antiretroviral drug. Antiretroviral usage was categorized as currently on, past use, or never used with particular emphasis on d-drugs and protease inhibitors. Statins and type 2 diabetic medications also were collected. Nadir CD4 cell count since HIV infection was self-reported.

HIV-sensory neuropathy definition

Trained personnel completed targeted, standardized neurological examinations to diagnose HIV-sensory neuropathy, which was defined by at least one clinical sign including reduced distal vibratory sensation, sharp sensation, and ankle reflexes as described previously [3,10]. Symptoms of HIV-sensory neuropathy (including loss of sensation, hyperalgesia, tingling, pain, or bilateral burning in the feet) were recorded but not required for HIV-sensory neuropathy diagnosis.

Clinical and metabolic laboratory measures

Random blood samples for glucose measurement were collected without regard to timings of prior meals in serum separator tubes. After clotting, serum was separated and sent to HNRC laboratory for nonfasting triglyceride (TRG), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and glucose measures. All blood pressure measurements were obtained based on established protocols [11,12]. Height and weight for calculating body mass index (BMI) were measured at entry. Diagnosis of type 2 diabetes was made based on postprandial blood glucose levels and self reported use of diabetes medications.

Statistical analysis

Univariable analyses were used to assess possible associations between TRG tertile, total cholesterol, LDL, HDL within HIV-positive patients with and without sensory neuropathy using chi-squared tests. Multivariable analysis was subsequently performed, relating log transformed TRG levels to neuropathy. Risk factors including demographic characteristics (age, height, ethnicity and sex), markers of HIV disease progression [current CD4 cell counts, CD4 nadir, length of HIV infection, plasma and cerebrospinal fluid (CSF) viral load], antiretroviral characteristics (d-drugs, statins and protease inhibitor use, HAART duration), type 2 diabetes, hepatitis C co-infection and history of alcohol or other drugs of abuse were evaluated for differences between those with and without neuropathy using chi-squared tests. Logistic regression was used to determine the unadjusted odds ratios (ORs) for each independent variable as a predictor for HIV-sensory neuropathy. Adjusted ORs were determined after correcting for all variables showing significant independent association with HIV-sensory neuropathy ($P < 0.05$). All analyses were performed using JMP statistical package (V8.0, SAS Institute Inc., Cary, North Carolina, USA).

Results

General characteristics of participants

HIV-positive individuals were mostly men (86%) with an average age of 47 years (Table 1). Most HIV-positive patients (75%) were under HAART regimens, and had complete virologic suppression as indicated by low median plasma and CSF viral loads ($1.7 \log_{10}$ copies/ml).

Additionally, most had substantial immune recovery as evidenced by a median current CD4 cell count of 458 cells/ μ l despite a relatively low median nadir CD4 cell count (105 cells/ μ l). HIV-positive patients had higher mean TRG levels (245 ± 242 mg/dl) than HIV-negative individuals (160 ± 97 mg/dl). Even after adjusting for age, $\log_{10}$ TRG levels showed significant association with HIV status ($P < 0.001$).

Prevalence and risk factors for HIV-sensory neuropathy

Among HIV-positive individuals, 27% had signs of sensory neuropathy compared to 10% of HIV-negative individuals. Among HIV-positive patients, sensory neuropathy was significantly associated in bivariate analysis, with older age ($P < 0.001$), height ($P < 0.001$), lower CD4 nadir ($P < 0.002$) and type 2 diabetes ($P < 0.01$). Likewise, protease inhibitor ($P < 0.02$) and statin use ($P < 0.01$) were associated with HIV-sensory neuropathy but not past or current d-drug exposure. Other risk factors like hepatitis C co-infection or history of alcohol abuse ($n = 336$) did not increase the risk for HIV-sensory neuropathy (Table 1). Related factors like sex, ethnicity, BMI, total cholesterol, LDL, HDL, absolute CD4, length of HIV infection and plasma viral load did not show any association with HIV-sensory neuropathy ($P > 0.05$ data not shown).

Log₁₀ TRG was independently associated with HIV-sensory neuropathy [OR 5.1, 95% confidence interval (CI) 2.4–11]. Since these measurements included nonfasting TRG we explored the association between a categorical classification of TRG (tertiles) and HIV-sensory neuropathy (Table 2). Compared with participants in the lowest TRG tertile (<142 mg/dl), participants in the second TRG tertile (>142 but <243; OR, 1.4, 95% CI 0.8–2.5) and the highest TRG tertile (≥244 mg/dl; OR 2.8, 95% CI 1.6–4.7) were at increased risk of sensory neuropathy. HIV-negative individuals showed a non-significant OR of 2.5 for developing sensory neuropathy (between highest and lowest TRG tertile) with a wide confidence interval (95% CI 0.3–18.2).

Potential HIV risk factors that could confound the relationship between TRG and HIV-sensory neuropathy included age, height, nadir CD4, type 2 diabetes, protease inhibitor and statin use (Table 1). After controlling for all these factors in a multivariable logistic regression model (Table 2), TRG levels remained strongly associated with increased risk for HIV-sensory neuropathy (OR 2.6, 95% CI 1.2–5.8).

Discussion

Elevated TRG levels increased the risk of HIV-sensory neuropathy by nearly three-fold between those in the lowest (<142) and the highest TRG tertile (≥244). After adjusting for concomitant clinical and demographic factors related to HIV-sensory neuropathy, the association of HIV-sensory neuropathy with TRG levels persisted. Medication use, specifically protease inhibitors, and statins was associated with both sensory neuropathy and triglyceride elevations. This was expected, as protease inhibitors have been associated with elevated TRG levels and HIV-sensory neuropathy [3], whereas statins, known to lower levels of cholesterol and TRG [13], are used to treat hypertriglyceridemia (hTRG) during CART therapy [14]. D-drugs may cause both sensory neuropathy and elevated TRG levels [5,10]. Despite this confounding, in multivariable models adjusting for these medications, elevated triglyceride levels remained associated with sensory neuropathy.

Lipodystrophy in HIV-infected patients (LDHIV) is associated with metabolic complications such as impaired glucose tolerance and hTRG [13–15]. Elevated serum TRGs correlate with the development of neuropathy in prediabetic patients without HIV. Mice fed high-fat diets have increased TRG-containing oxidized LDLs and systemic and nerve oxidative stress and develop reduced nerve conduction velocity (NCV) and sensory deficits prior to impaired glucose tolerance [16,17]. Our study extends these observations found in animals to demonstrate that hTRG is a risk factor for neuropathy in HIV-infected humans.

We previously reported a positive association between elevated fasting TRG levels and HIV-sensory neuropathy in a HIV-positive cohort (CHARTER). The present study amplifies on this association in the following ways. First, whereas the previous study examined fasting TRG levels in a much smaller HIV-positive cohort (*n*=130), we now report similar risk relationship for nonfasting TRG which is more convenient to procure, in larger cohort of HIV-positive and HIV-negative participants (*n*=491 HNRC). Secondly the previous study cohort consisted of a very high percentage of d-drug users (70%), which could obscure other risk factors associated with HIV-sensory neuropathy, whereas d-drug use was only 30% in this current cohort.

Also, the present study used multivariable logistic regression models to adjust for concurrent HIV-sensory neuropathy risk factors, whereas the previous study applied univariable analyses. Finally, the present study included lipid-lowering statins among the variables modeled, whereas the previous study did not.

Other markers that correlated with HIV-sensory neuropathy in this study like age, height, nadir CD4, use of protease inhibitors were recognized in prior studies [2,8,10,15–17]. However, several other risk factors identified in other studies were not found in our cohort. Exposure to d-drugs was not a risk factor for HIV-sensory neuropathy, possibly because only 30% of our cohort had a history of d-drug use. We also found no association of sensory neuropathy with type 2 diabetes in HIV-negative volunteers, which might be due to a very small number of diabetics in this cohort [10,18].

Pathologically, HIV-sensory neuropathy is characterized by distal axonal degeneration of small myelinated and unmyelinated nerve fibers [19]. Various mechanisms have been proposed in this regard. Mutations in mitochondrial DNA have been suggested as one of the primary mechanism for sensory neuropathy [20]. High TRG levels might lead to alteration in mitochondrial energy metabolism and membrane permeability. Alteration of mitochondrial functions leads to release of hydrogen peroxide and peroxynitrites, resulting in degeneration of nerve fibers [21]. A strong association between compromised microvascular blood flow with sensory neuropathy in type 2 diabetes has also been reported [22].

Limitations of this study include first its observational cross-sectional design, which limits causal inference. Nevertheless, prior studies of non-HIV-infected individuals have shown high serum TRG to be a risk factor for progression of diabetic sensory neuropathy and animal studies, as noted previously, support a causal link [23,24]. It is still possible that elevated TRG is a surrogate for another, underlying, unmeasured factor, such as mitochondrial dysfunction, oxidative stress or microvascular compromise, which serves as the causal link to neuropathy. An interventional study to reduce mitochondrial dysfunction and these other disturbances would provide a useful test of this hypothesis. Secondly the participants were enrolled at a single center. To address this limitation, future studies might assess a more broadly representative sample of HIV-positive patients. TRGs in most studies are measured in the fasting state because of its elevation after food intake [25]. However, nonfasting TRG levels may be a better predictor of future cardiovascular events [25,26].

The strengths of this study include the assessment of HIV-sensory neuropathy by trained personnel using standardized, quality-controlled methods and thorough accounting for potential confounding factors such as demographic variables, HIV and HCV infections, and alcohol and other drug exposures.

These findings illustrate the pathogenic complexity of HIV-sensory neuropathy to which not only HIV infection, but also its treatment, is a major contributor. Since increased TRG levels were identified as a major risk for HIV-sensory neuropathy, interventions leading to reduction of TRG levels [27] could reduce incidence of HIV-sensory neuropathy, a possibility that should be explored in future studies.

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Table 1

Participants, demographics, disease characteristics co-morbidities and concomitant medications.

	HIV-negative	HIV-positive No SN	HIV-positive SN	P value No SN versus SN
<i>N</i>	55	317	119	
Age (years) ^a	49.3 (11.1)	45.2(9.8)	51.6 (9.9)	<0.0001
Height (inches)	67.7 (3.4)	67.4 (3.8)	69.2 (3.5)	<0.0001
Male	67%	72.90%	85.70%	
CD4 cell count ^b	NA	493(307–689.5)	458 (279–637)	<0.25
CD4 nadir ^b	NA	178 (50–293.5)	105 (18–219)	<0.002
PI	NA	40.10%	52.10%	<0.02
D-drug ever	NA	30.60%	29.70%	<0.85
Statin ^c	<i>n</i> = 35 (28%)	<i>n</i> = 48 (23.4%)	<i>n</i> = 33 (37.9%)	<0.01
Type 2 diabetes ^d	3	<i>n</i> = 19 (6%)	<i>n</i> = 17 (14.2%)	<0.01
Alcohol abuse ^e	39%	<i>n</i> = 109 (44.9%)	<i>n</i> = 47 (50.5%)	<0.35
HCV-positive ^f	0	<i>n</i> = 19 (11%)	<i>n</i> = 7 (9.7%)	<0.8

HCV, hepatitis C virus; PI, protease inhibitor; SN, sensory neuropathy.

Note: Out of total number of patients with neuropathy 24.7% were asymptomatic, whereas 75.3% showed symptoms of neuropathy. Age, height, nadir CD4 cell count, type 2 diabetes and use of PIs and statin were significantly ($P<0.05$) associated with risk of HIV-SN.^aMean SD.^bMedian (interquartile range).^cAmong individuals with information on statin use *n* = 35 for HIV-negative and *n* = 81 for HIV-positive.^dElevated glucose (>180mg/dl PP) self-report and or under antidiabetic medication (*n*=36).^eTotal number of HIV-positive participants *n* = 336 among which *n* = 47 showed a positive co-relation between neuropathy and history of alcohol abuse.^fTotal number of participants *n* = 245 among which *n* = 26 were HCV-positive.

Table 2

Effect of triglyceride on HIV-sensory neuropathy.

Triglyceride tertile (mg/dl)	N	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
		OR [CI]	OR [CI]	OR [CI]	OR [CI]	OR [CI]	OR [CI]	OR [CI]
141	144	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
142–243	145	1.4 [0.8–2.5]	1.4 [0.8–2.5]	1.4 [0.8–2.5]	1.3 [0.7–2.4]	1.7 [0.8–3.7]	1.7 [0.8–3.7]	1.6 [0.7–3.6]
244	145	2.8 [1.6–4.7]	2.5 [1.4–4.5]	2.5 [1.4–4.5]	2.3 [1.3–4.1]	2.6 [1.3–5.4]	2.7 [1.4–5.5]	2.6 [1.2–5.8]

CI, 95% confidence interval; OR, odds ratio.

Model 1: Neuropathy unadjusted. Model 2: Neuropathy adjusted to age. Model 3: Neuropathy adjusted to age and protease inhibitor. Model 4: Neuropathy adjusted to age, protease inhibitor and CD4 nadir. Model 5: Neuropathy adjusted to age, protease inhibitor, CD4 nadir and statin use. Model 6: Neuropathy adjusted to age, protease inhibitor, CD4 nadir, statin use and type 2 diabetes. Model 7: Neuropathy adjusted to age, protease inhibitor, CD4 nadir, statin use, type 2 diabetes and height. Increased triglyceride levels were significantly associated with HIV-sensory neuropathy independent of concomitant risk factors.