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Peripheral Neuropathy in Primary HIV Infection Associates with Systemic and CNS Immune Activation

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Abstract

Background—Peripheral neuropathy (PN) is a frequent complication of chronic HIV infection. We prospectively studied individuals with primary HIV infection (PHI, <1 year after transmission) to assess the presence of and laboratory associations with PN in this early stage.

Methods—Standardized examination and analysis of blood and cerebrospinal fluid (CSF) was performed in participants with laboratory-confirmed PHI. PN was defined as ≥1 of the following unilateral or bilateral signs: decreased distal limb position, vibration, or temperature sense, or hyporeflexia; symptomatic PN (SPN) as presence of these signs with symptoms. Analysis employed nonparametric statistics.

Results—20/58 (35%) antiretroviral-naïve male subjects without diabetes evaluated at a median 107 days post HIV transmission (dpt) met criteria for PN. 13/20 (65%) of PN subjects met criteria for SPN; 6/20 (30%) had bilateral findings. PN subjects and no PN subjects (NPN) did not differ in median age, dpt, blood CD4 or CD8 counts, CSF or plasma HIV RNA levels, CSF white blood cell counts, or CSF:blood albumin ratio. PN and SPN subjects had elevated CSF neopterin (p=0.003 and p=0.0005), CSF MCP-1 (p=0.006 and p=0.01) and blood neopterin (p=0.006 and

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p=0.009) compared to NPN. PN subjects had a higher percentage of activated phenotype CSF CD8+ T lymphocytes than NPN subjects (p=0.009).

Conclusions—Signs of PN were detected by detailed neurologic exam in 35% of men enrolled in a neurological study at a median 3.5 months after HIV transmission. PN during this early period may be mediated by systemic and nervous system immune responses to HIV.

Keywords

HIV; peripheral neuropathy; cerebrospinal fluid; immune activation

Introduction

HIV-1 (HIV) affects both the central nervous system (CNS) and peripheral nervous system (PNS)[1,2]. Nervous system infection with HIV produces a range of clinical disorders, with peripheral neuropathy as a frequent neurological complication[3]. Although many of the end-stage complications of advanced AIDS and immunosuppression are prevented or ameliorated by the use of potent combination antiretroviral therapy (ART), neurological abnormalities persist as detected by reduced performance on neuropsychological testing[4,5], which may reflect damage to both the PNS and the CNS[2,6]. The extent of early PNS dysfunction during primary HIV infection (PHI) is unknown, though understanding the frequency and mechanism of PNS involvement may provide therapeutic approaches to neuroprotection in HIV-infected persons.

A distal sensory polyneuropathy (DSP) is the most common type of peripheral neuropathy seen in chronic HIV infection or with neurotoxic ART, presenting with symptoms of distal numbness and paresthesias, and signs of absent or decreased deep tendon reflexes[7]. The exact pathogenesis of HIV-DSP is unknown. Macrophage activation and pro-inflammatory cytokines associate with neurological disease development, and are implicated in the immunopathogenesis of HIV-DSP[8]. Pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-6 have been detected in the dorsal root ganglia (DRG) of HIV-infected patients, suggesting inflammation-mediated neuronal damage[9,10]. However, studies have been limited to patients with AIDS, and little is known about the inflammatory mediators of HIV-DSP in early infection. Although numerous case reports have described peripheral nerve abnormalities including DSP, demyelinating neuropathies, and focal neuritis following initial seroconversion[11–13], systematic data assessing when peripheral nerve abnormalities first develop in recent HIV infection and what underlying pathophysiology causes such damage is lacking.

In the first weeks and months of HIV infection, cerebrospinal fluid (CSF) HIV RNA and intrathecal immune activation can be readily detected in untreated patients[14–16]. We hypothesized that peripheral neuropathy may be present during PHI, and that correlations may exist between levels of infectious and inflammatory biomarkers and signs of peripheral neuropathy in this setting. To assess whether specific markers of viral replication and immune activation, including monocyte chemoattractant protein-1 (MCP-1), neopterin, interferon gamma induced protein-10 (IP-10), and activated CD4+ and CD8+ T lymphocytes and monocytes associate with peripheral neuropathy in early HIV infection, we

performed a cross-sectional neurological study of ART-naïve subjects during the first year of HIV infection.

Methods

Study participants

Baseline visits from a longitudinal neurological study of PHI, defined as within the first 12 months after HIV transmission, were analyzed. Timing of infection was confirmed by a combination of antibody seroconversion, nucleic acid testing, or less sensitive enzyme immunoassay result[17], and days post HIV transmission (dpt) was defined by estimating infection as 14 days prior to the onset of seroconversion symptoms or, in those with asymptomatic seroconversion, as the date halfway between the last negative and first positive HIV test[18,19]. Subjects were excluded if they had diabetes, thyroid disease, or prior ART exposure. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards at University of California San Francisco (USCF) and Yale.

Clinical evaluation

Presence of peripheral neuropathy (PN) was determined through a neurologist's (RWP, MG, EH, or SS) examination and recording of signs and symptoms according to a standardized UCSF Macro Neurologic examination (MacroNeuro) created for the AIDS Clinical Trial Group. PN was defined as presence of unilateral or bilateral signs of decreased position, vibration, or temperature sense at great toes, or presence of distal pain or tingling on examination with or without hyporeflexia or absent or decreased ankle jerks. Diminished vibration was documented as absent sensation of vibration of a 128 Hz tuning fork over a distal bony joint, or reduction of vibration duration compared to testing on the sternum of the subject and to that detected by the examiner. A reduction in 'cold' sensation from the flat portion of the tuning fork in the distal limbs compared to face and/or proximal limbs was considered a temperature deficit. Symptomatic peripheral neuropathy (SPN) met more stringent criteria of having aforementioned signs as well as symptoms including numbness and paresthesias. Information about alcohol use, abuse (determined according to modified 'CAGE' questions) and intravenous (IV) drug use was ascertained by standardized written inventories. Subjects underwent concurrent general medical, neuropsychological, and laboratory assessments. Neuropsychological testing included dominant hand grooved pegboard, non-dominant hand finger tapping, digit symbol test, and timed gait. Z scores were calculated for each test using age-adjusted norms, and were averaged to a summary NPZ-4 score.

Specimen sampling and processing

Laboratory assessments included blood testing and lumbar puncture. CSF total white blood cell (WBC), protein, albumin, blood albumin, CD4+ and CD8+ counts by flow cytometry were measured on fresh samples. Cell-free CSF and blood plasma were also aliquoted and stored within 6 hours of collection in −70°C freezers monitored daily for temperature using NIST-certified thermometers.

Measurement of soluble immune activation

Concentrations of CSF and blood neopterin, IP-10 and MCP-1 were measured in previously frozen samples at UCSF or in the laboratory of Dr. Fuchs by commercial immunoassays (BRAHMS Aktiengesellschaft).

Measurement of cellular immune activation

Multiparameter flow cytometry was used to measure the percentage of CD38 and HLA-DR double positive CD8+ and CD4+ T lymphocytes in a subset of CSF and whole blood samples using previously described methods[20,21]. Lymphocyte activation antibody-dye panels were switched halfway through the study, though the two panels were compared in analysis and confirmed to have consistent T lymphocyte activation measures. A further subset of samples was analyzed by flow cytometry for monocyte activation, identifying CD3 negative cells with a CD14+CD16+ phenotype. Blood samples were stained with fluorescence minus one (FMO) controls in which one antibody was omitted. An unstained control and single stained samples were also prepared as compensation controls. Samples were run on a FACS DIVA (BD Biosciences) and analyzed with FlowJo (TreeStar, Ashland, OR).

Virological Methods

HIV RNA levels were measured in previously frozen cell-free CSF and plasma using the ultrasensitive (50 copies/mL lower limit of detection) Amplicor HIV Monitor (version 1.5; Roche Molecular Diagnostic Systems, Branchburg, NJ), or the Abbott RealTime HIV-1 (Abbot Laboratories, Abbot Park, IL, USA) assays. Paired blood and CSF measurements were made using the same assay, in the same PCR run.

Statistical Analysis

Descriptive statistics were performed using Stata/SE 11.0 (StataCorp LP, College Station, TX). Nonparametric Mann-Whitney rank sum test compared group differences between PN and NPN, as well as subgroup differences between SPN and NPN. Fisher's exact test compared differences between categorical variables. A regression model compared group differences after adjusting for age, alcohol abuse, and race.

Results

Study Participant Characteristics

Clinical and laboratory characteristics of study subjects are presented in Table 1. Subjects were previously healthy men with a median age of 36 years and CD4+ T cell count of 575 cells/μL evaluated at a median estimated 107 dpt. Subjects had normal basal metabolic indices (BMI) and showed no evidence of nutritional deficiency. Additional demographic data including ethnicity, history of IV drug use, alcohol use, and hepatitis C infection status are presented in Table 1.

Clinical and Demographic Associations with Peripheral Neuropathy in Primary Infection

20 of 58 (35%) PHI subjects had signs of peripheral neuropathy (designated ‘PN subjects’) upon neurologic examination. There was a trend towards PN subjects being older with a median age of 40 years compared to 34 years in subjects with no peripheral neuropathy (NPN, p=0.05). There was no significant relationship between history of alcohol abuse and signs of peripheral neuropathy (p=0.05). Of the 20 PN subjects, 6 subjects had bilateral findings, 7 subjects had unilateral findings, and in the remaining 7 subjects, laterality was not specified. Neuropsychological performance (NPZ4) was not different between the PN and NPN groups (−0.24, IQR−0.70–0.22 vs. 0.02, IQR −0.50–0.65, p=0.18). There was no difference in dpt between the two groups. The PN group showed no significant difference compared to the NPN group in absolute blood CD4+ (582 cells/μL, IQR 408–729 vs. 558 cells/μL IQR 453–715, p=0.82) and CD8+ T cell counts (1019 cells/μL, IQR 674–1543, I vs. 901 cells/μL, IQR 701–1202, p=0.59). 13 of the 20 PN subjects (65% of PN, 22% of total) also had symptoms of peripheral neuropathy (SPN). Typical symptoms included “foot tingling and numbness.” There were no demographic differences identified between NPN and SPN subjects.

Laboratory Associations with Peripheral Neuropathy in Primary Infection

Median plasma HIV RNA levels and CSF HIV RNA levels were similar between PN and NPN groups, as well as between SPN and NPN groups. CSF WBC count (8.00 cells/μL, IQR 2.00–10.00 vs. 6.00 cells/μL, IQR 2.00–12.00, p=0.48) and albumin ratios (4.96, IQR 4.46–6.53 vs. 5.47, IQR 4.23–8.25, p=0.76) were similar between PN and NPN subjects. Median levels of blood neopterin (17.9 nmol/L, IQR 15.4–25.3, vs. 12.1 nmol/L, IQR 8.8–20.0, p=0.006), CSF neopterin (13.7 nmol/L, IQR 8.0–21.9, vs. 8.1 nmol/L, IQR 5.2–9.5, p=0.003), CSF MCP-1 (620 pg/mL, IQR 534–780, vs. 477 pg/mL, IQR 373–643, p=0.006), and IP-10 (910 pg/mL, IQR 401–1749, vs. 530 pg/mL, IQR 323–907, p=0.09) in the PN subjects were elevated as compared to the NPN subjects (Figure 1A–E). Additional analysis adjusted for age, alcohol use, and race showed continued significant elevation of CSF neopterin (p=0.02) and blood neopterin (p=0.008) in PN compared to NPN subjects. There remained a trend for MCP-1 to be elevated in PN subjects, but the association was not statistically significant (p=0.05).

Flow cytometric analysis of CD8+ T lymphocyte activation revealed similar median percentage of activated CD38+/HLADR+ CD8+ T lymphocytes in PN subjects in blood (p=0.23) but elevated percentage in the CSF compartment (77.6%, IQR 69.4–86.8, vs. 60.9%, IQR 49.7–68.0, p=0.004, Figure 2A–D) compared to NPN subjects. There were no differences in percentages of activated CD4+ T lymphocytes or activated CD14+CD16+ monocytes in blood or CSF between PN and NPN.

When PN only subjects were excluded from the analysis, and CSF and blood samples for inflammatory biomarkers were compared between SPN and NPN subjects, elevated levels of CSF neopterin (14.3 nmol/L, IQR 5.9–29.7 vs. 8.1 nmol/L, IQR 4.4–9.5, p=0.0005), CSF MCP-1 (623 pg/mL, IQR 330–791 vs. 477 pg/mL, IQR 208–643, p=0.01), CSF IP-10 (1063 pg/mL, IQR 432–2242, vs. 530 pg/mL, IQR 327–907, p=0.03), and blood neopterin (17.7 nmol/L, IQR 10.8–32.4, vs. 12.1 nmol/L, IQR 4.3–12.1, p=0.009) were found in the SPN

group. Percentage of activated CD4+ T lymphocytes and monocytes did not differ between the SPN and PN subjects in either compartment.

Discussion

Peripheral neuropathy is a frequent neurological disorder reported in HIV, classically in the setting of chronic untreated HIV infection or following exposure to certain antiretroviral medications. However, we found that signs (35%), or signs and symptoms (22%), of peripheral neuropathy were evident in a cohort of ART-naive subjects recruited to a neurological study at a median of 3.5 months after initial HIV transmission. We further examined mechanisms for peripheral nerve dysfunction identified during this stage, revealing that markers of systemic and CNS immune activation are elevated in subjects with signs of neuropathy (PN) compared to those with no signs of neuropathy (NPN).

Disorders of the PNS manifesting during PHI, typically around the period of HIV seroconversion, are well-described in case reports and series, and include acute inflammatory demyelinating peripheral neuropathies, meningoradiculitis and ataxic neuropathy[12,22,23]. However, subtle signs and symptoms of peripheral neuropathy during PHI have not been systematically studied. The pathogenesis of classic HIV-DSP is not clearly elucidated, but is thought to be due to a combination of direct viral toxicity and immune activation. Increased monocyte-macrophage markers, lymphocyte and macrophage infiltration, and cytokine expression are detected in the peripheral nerves and DRGs of patients with DSP in AIDS[24], with resulting distal demyelination and axonal degeneration in a “dying back” pattern. The immunologic response to HIV begins in early disease with chemokine elevation, including MCP-1 and IP-10, as well as the macrophage activation marker neopterin, in the blood and CSF of HIV patients with normal CD4+ T cell counts, and even during PHI[25,26].

We found high rates of peripheral neuropathy in our cohort of PHI subjects. As subjects with symptomatic seroconversion and neurologic symptoms may have been more likely to enroll in the study, it is possible that the prevalence of peripheral neuropathy in our cohort is higher than in all individuals with PHI. This may be one contributing factor to differences between our findings and that of a previous study, which observed a much lower rate of neuropathy (1.5%) in military recruits with HIV infection, mostly prior to advanced AIDS[27]. This discrepancy may also be due to different thresholds in assessment and reporting. It is possible that Barohn et al.’s examinations were performed to detect peripheral neuropathy affecting military performance, and that mild or subclinical signs were not recorded. In contrast, our diagnostic thresholds were used to detect and document evidence of neuropathy for research purposes. Furthermore, our subjects presented at an earlier stage of infection, with an overall median CD4+ T cell count of 575 cells/uL and none having a CD4 count <200, while in Barohn et al.’s study, 7.8% (62/798) had a CD4 count <200. The period of early infection characterizing our cohort is associated with rapid HIV virema, acute systemic and CNS immune activation, and well-documented occurrence of symptomatic peripheral nerve disorders. These disorders are poorly understood, but are likely immune-modulated, and may improve after this early dynamic period of immune response initiation. Therefore,

it is plausible that PHI might be characterized by a higher prevalence of peripheral neuropathy than early chronic HIV infection.

Plasma HIV RNA and CD4+ T cell count associate with and are predictive of the development and severity of HIV-associated peripheral neuropathy in chronic infection[28,29]. In contrast, we found no difference in these factors between PN and NPN PHI subjects, suggesting that they may not be crucial mediators of PNS involvement in early infection. Additionally, HIV transcripts and proteins have been detected in DRG neurons and surrounding satellite cells in subjects with peripheral neuropathy and HIV-DSP[30] However, it is generally believed that HIV replication in peripheral nerves is scarce. CSF HIV RNA, CSF total protein levels (a measurement of all detected CSF proteins indicative of blood brain barrier, BBB, integrity), and CSF:blood albumin ratios (a highly specific marker of BBB integrity) were similar between PN and NPN subjects, suggesting that the viral burden measurable within the nervous system and BBB penetrance may not contribute to neuropathy during PHI.

Amplified immune activation characterized our subjects with signs of peripheral neuropathy. CSF markers have been previously implicated in advanced stages of HIV neurological disease progression: CSF neopterin rises along with CNS HIV disease severity and decreases following ART[31]; levels of IP-10 positively correlate with the presence of HIV-associated dementia (HAD)[32]; and elevated MCP-1 is detected in the brain and CSF of subjects with HIV-encephalitis and HAD[33,34]. Our results support the premise that immune activation is crucial to peripheral neurological dysfunction in HIV. The chemoattractants MCP-1 and IP-10 likely escalate disease through augmentation of viral replication in already-infected cells, and enhance local inflammation by lymphocyte and monocyte recruitment[35,36]. With increased monocyte activation and macrophage presence, HIV cellular transmission perpetuates, and infection leads to macrophage priming, induction of pro-inflammatory cytokines and TNF-α, leading to neuronal dysfunction. Furthermore, in rat models, endothelial cells that supply DRGs are highly fenestrated, suggesting that this area of the PNS may be particularly vulnerable to toxic effects of circulating activated monocytes and pro-inflammatory cytokines[37].

Our findings of increased CNS inflammation in the presence of peripheral neuropathy may be explained through alternative models: HIV concurrently infects both the CNS and PNS, and our detected associations are coincidental, or, alternatively, peripheral neuropathy induces secondary changes within the CNS. In support of the former, studies of SIV-infected macaques at 12-weeks post inoculation have detected increased monocyte infiltration of DRGs, as well as decreased DRG neuronal density and conduction velocity in the absence of neuritis or damage to myelinated peripheral nerves[38]. Thus, though there may be an association between central and peripheral immune activation, the presence of CNS and PNS lesions may not correlate. Alternatively, in HIV-DSP, macrophage secretion of pro-inflammatory molecules within the nerve may lead to CNS immune activation. In support of this, perineural application of the HIV envelope glycoprotein gp120 to rat sciatic nerves leads to TNF-α expression in the DRG and glial cells in the spinal cord[39]. Pro-inflammatory cytokines may promote a paracellular route for HIV-1 across the BBB, facilitating HIV infection of the CNS[40]. MCP-1 contributes to blood spinal cord barrier permeability

following peripheral nerve injury, and individuals with mutant MCP-1 genotypes have increased risk of HAD and accelerated disease progression[41,42]. Therefore, a cycle of immune activation and subsequent overproduction of pro-inflammatory cytokines and chemokines may allow for further cell trafficking from the periphery into the CNS to create further inflammation and neuronal damage.

In our participants, flow cytometry analysis of T lymphocyte activation demonstrated elevated percentages of CD38+/HLA-DR+ CD8+ T lymphocytes in the CSF of PN subjects. HLA-DR and CD38 expression on CD8+ T lymphocytes correlates with clinical stages of HIV disease, with simultaneous expression of both increasing in symptomatic disease[43]. MHC class II molecule HLA-DR expression increases in CD8+ T lymphocytes upon HIV seroconversion and remains stable, while expression of CD38 levels on CD8+ lymphocytes increases throughout disease and is thought to be a predictor of AIDS progression and death[44,45]. The percentage of CD38+ and HLA-DR+ CD8+ T lymphocytes rises progressively with advancing HIV disease in pre-ART subjects[46], while ART decreases the level of blood CD38+/HLA-DR+ co-expression on CD8+ T lymphocytes, even in subjects only partially responsive to treatment[47]. Our findings suggest that increased migration to or accumulation of ‘activated’ phenotype CD8+ T lymphocytes within the CSF pathologically associates with peripheral neuropathy. This is the first study to examine T lymphocyte activation in the CNS compartment in relation to clinical neurological disease in HIV. Whether these findings indicate that peripheral neuropathy is associated with processes accelerating disease progression within the nervous system, or another mechanism of injury warrants further study.

We examined the PN group using more stringent criteria of both signs and symptoms of peripheral neuropathy, identifying 13 SPN subjects. When compared with our NPN group, elevations in inflammatory markers of CSF neopterin, CSF MCP-1, CSF IP-10, and blood neopterin were noted. The lack of association between presence of SPN and monocyte and T lymphocyte activation levels could be due to lower samples in this subgroup, reducing our power to detect significant differences from NPN. The consistency in elevation of inflammatory markers in the setting of symptomatic disease supports the explanation that peripheral neuropathy is mediated in part by an inflammatory response. Animal studies have demonstrated elevated pro-inflammatory cytokines in rats experiencing sustained allodynia and hyperalgesia following intrathecal and perineural gp-120 administration, which is thought to be neurotoxic and lowers the excitation threshold[48–50]. This aberrant immune response may lead to neuronal hyperexcitability, creating exaggerated pain states that explain symptomatic peripheral neuropathy seen in early infection.

Limitations of this study include the cohort homogeneity, since all subjects were ART-naïve men who have sex with men (MSM) with PHI, within a focused range of age and education. Although this limits generalizability, it allows for the examination of the effects of early HIV with reduced confounders such as potential toxicities of ART. Furthermore, though we did not perform electromyography and nerve conduction studies (EMG/NCS) in our subjects to electrophysiologically characterize neuropathy, our diagnostic criteria have been used previously in studies examining HIV peripheral neuropathy[51,28]. Importantly, potential confounders to the analysis need to be considered, and the PN subjects had elevated rates of

alcohol abuse compared to NPN subjects. Previous studies have shown that age[52], alcohol abuse[53], and ethnicity[54] are risk factors for peripheral neuropathy. Our adjusted analyses suggest that though these factors may contribute to and be confounders to the finding of peripheral neuropathy, in the context of elevated CNS and systemic immune activation, they are unlikely to entirely explain our finding of a notable relationship between immune activation and the presence of peripheral neuropathy. Peripheral neuropathy may also develop in the setting of nutritional deficiencies[55]. Although we did not measure vitamin levels in subjects, none had advanced HIV infection, food insecurity, signs of wasting, or low BMI. Thus, the presence of vitamin deficiency contributing to nutritional neuropathy seems doubtful. Finally, the results of this study are limited to the timeframe of PHI. Longitudinal follow up of our cohort is underway to study the natural history of peripheral neuropathy in early infection and to investigate whether neuropathy during early infection is transient or progressive.

Previous studies have examined the prevalence of peripheral neuropathy in HIV-infected individuals on ART, in subjects with longstanding, chronic HIV infection, or AIDS. This is the first study to examine the prevalence of peripheral neuropathy among ART-naïve individuals within the first months after HIV acquisition. We found a high rate of peripheral neuropathy among PHI subjects that correlated with increased levels of systemic and intrathecal pro-inflammatory markers. Recognition of PHI as an essential period of immune activation associated with peripheral neuropathy and neurological disorders may provide rationale for more aggressive screening for recent HIV infection, and early institution of ART and possibly immunomodulatory therapy during this early eriod.

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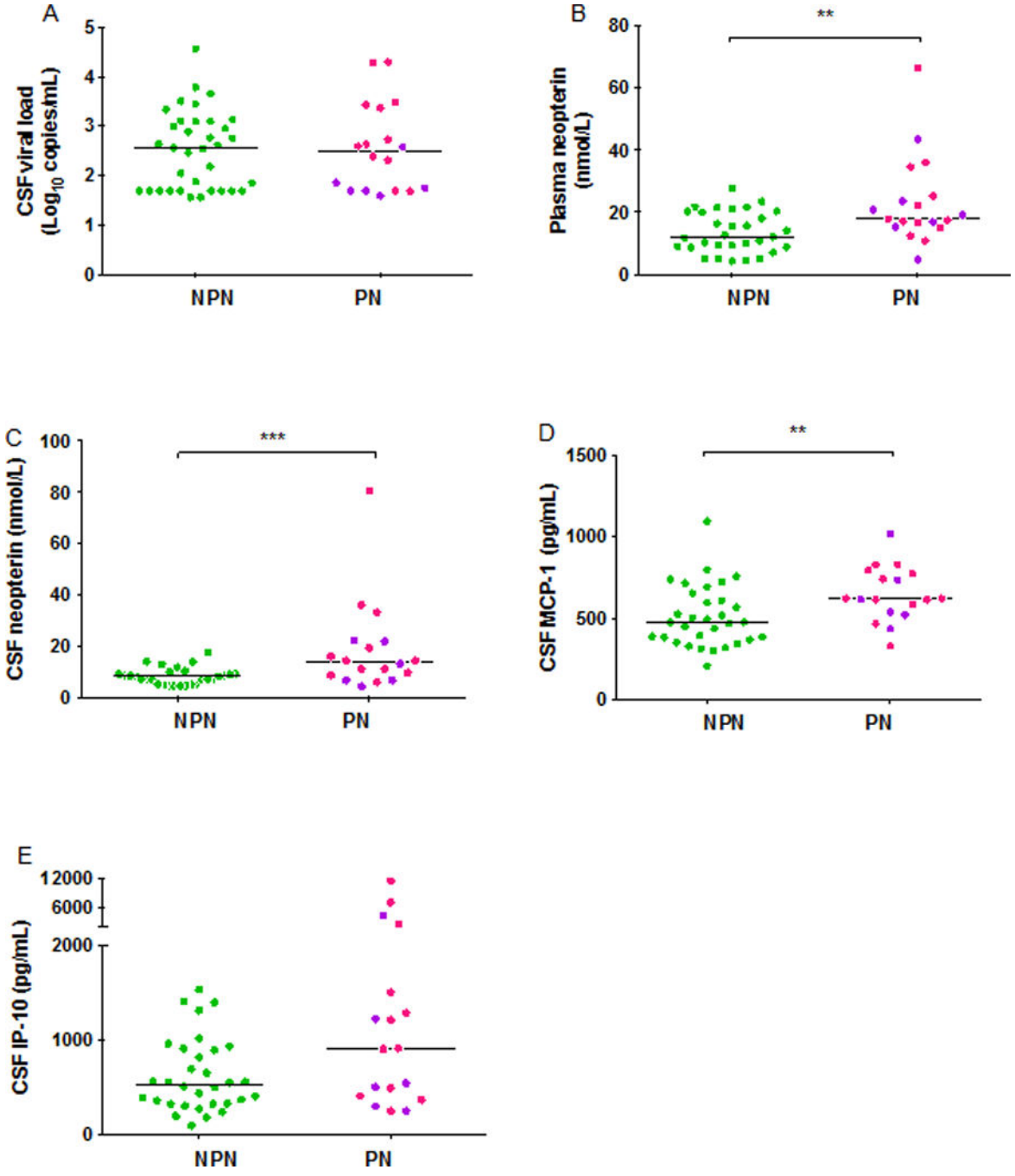

Figure 1A–E. Markers of immune activation in blood and CSF of PHI subjects with and without signs of peripheral neuropathy

A) CSF viral load B) blood neopterin C) CSF neopterin D) CSF MCP-1 E) CSF IP-10. A single asterix represents P-value <0.05, double asterixes represent P-value <0.01, and triple asterixes represent P-value <0.005. Significant differences were detected between NPN and PN in blood neopterin (B, p=0.006), CSF neopterin (C, p=0.003), and CSF MCP-1 (D, p=0.006). Differences noted in (B) and (C) remained significant when single outlier was excluded. Solid bars indicate medians. Pink symbols indicate SPN subjects, purple symbols

indicate PN subjects. Approximate reference values for blood neopterin <8.8 nmol; CSF neopterin <5.8 nmol; MCP-1: <500 pg/mL; IP-10 <250 pg/mL.

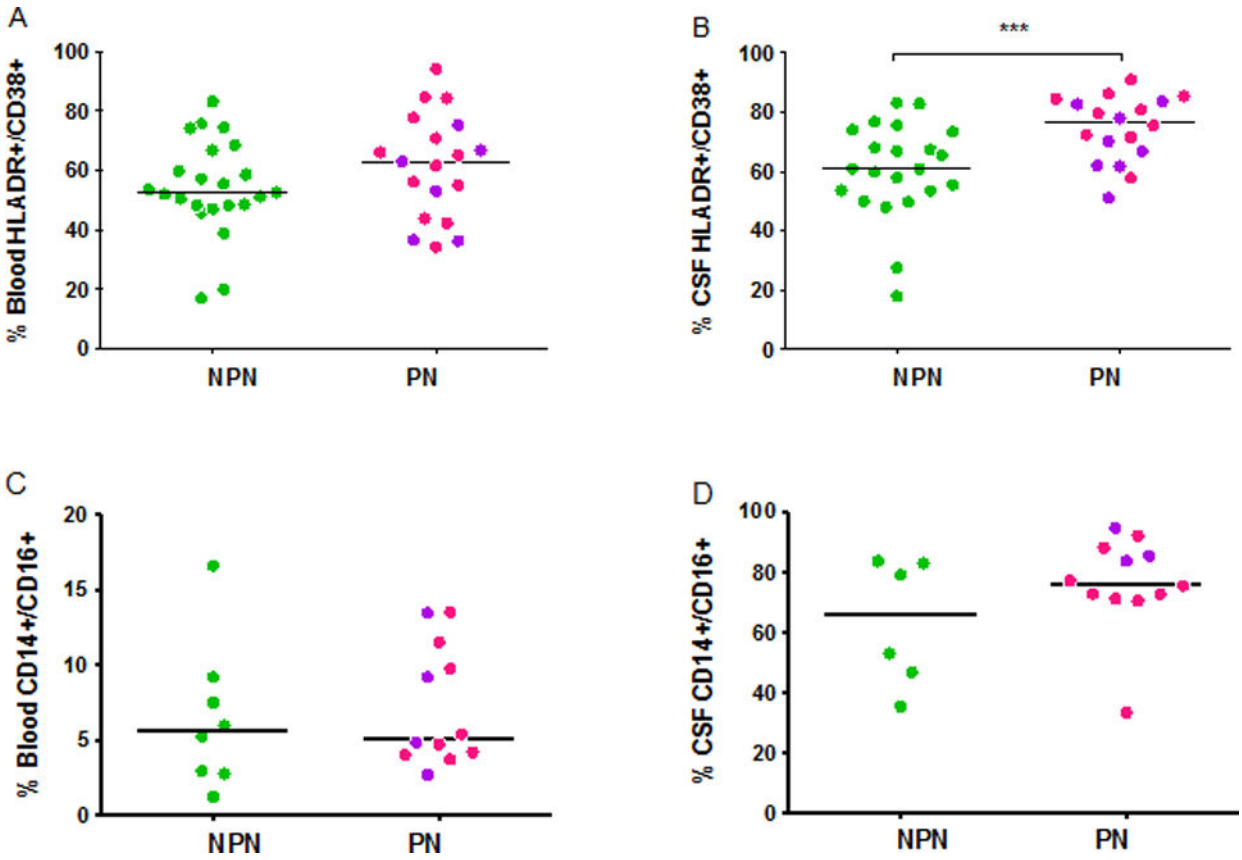

Figure 2A–D. Cellular immune activation in PHI subjects with and without signs of peripheral neuropathy

A) Blood CD38+/HLADR+ CD8+ T lymphocytes B) CSF CD38+/HLA-DR+ CD8+ T lymphocytes C) Blood CD14+/CD16+ monocytes D) CSF CD14+/CD16+ monocytes. A single asterix represents P-value <0.05, double asterixes represent P-value <0.01, and triple asterixes represent P-value <0.005. PHI subjects with signs of peripheral neuropathy (PN) had a significantly elevated proportion of activated (CD38+/HLADR+) CD8 T lymphocytes in CSF (B, p=0.004) compared to those without peripheral neuropathy (NPN).

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Table 1

Clinical and demographic characteristics of study participants by group.

	Overall Median	NPN	PN	SPN	*p* value
Number		38	20	13	
Age (years)	36	34 (27–42)	40 (31–47)	37	0.05* 0.33ψ
Years of education	16	16	15	14	0.13* 0.06ψ
Days post HIV transmission	107	104 (65–188)	125 (74–164)	137 (72–172)	0.87* 0.91ψ
CD4+ T cellcount (cells/ul)	575	558 (408–729)	582(453–715)	601 (483–755)	0.83* 0.41ψ
CD8+ T cell count (cells/ul)	985	701 (513–1202)	1019 (674–1543)	1053 (736–1635)	0.59* 0.33ψ
Plasma HIV RNA (log_{10} copies/mL)	4.45	4.37 (3.94–4.77)	4.79 (3.17–5.18)	4.82 (3.00–5.28)	0.29* 0.25ψ
Race/Ethnicity White, n (%)		29 (49.2)	10 (17.2)	8 (13.8)	0.08* 0.35ψ
History of IV drug use Yes, n (%)		27 (46.6)	16 (27.6)	10 (17.2)	0.72* 0.52ψ
History of alcohol use Yes, n (%) Unknown, n (%)		12 (20.7) 3 (7.9)	13 (22.4) 0	8 (13.8) 0	0.05* 0.65ψ
Hepatitis C infection status					

	Overall Median	NPN	PN	SPN	*p* value
Yes, n (%)		1 (2.6)	0	0	
Unknown, n (%)		5 (13.2)	0	0	

Abbreviations:
NPN = no peripheral neuropathy. PN = peripheral neuropathy. SPN = symptomatic peripheral neuropathy.
Values are presented as medians (IQR) unless otherwise noted.

[*] NPN vs. PN

[ψ] SPN vs. PN