Original Paper

# Considerations About Risk Factors for Peripheral Neuropathies in Romanian HIV-Infected Patients

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**ABSTRACT:** Purpose: The study aims at detecting risk factors for developing peripheral neuropathy in Romanian HIV infected subjects. Material/Methods: retrospective study (january 1990-january 2009) who analyzed data from patients hospitalized in the Regional Center Craiova. We have compared 26 patients (group N) diagnosed with peripheral neuropathy with 40 patients (group C) without neuropsychological sufferings, randomly selected. We have analysed: age, height, HIV mode of transmission, AIDS status, the average and nadir of $CD_4$ lymphocytes, the mean viral load, the average duration of antiretroviral treatment (ART), use and duration of use of d-drugs, the presence of certain coinfection, diabetes or ethanol abuse. Results: the following differences were statistically significant: age (31,54±14,64 vs 23,9±12,03 years, p=0.024), HIV mode of transmission (parenteral/sexual: 13/13 vs 28/8, p = 0.044), the monitoring time duration (5,31±3,77 vs 7,75±5,4 years, p=0.043), median ART duration (37,2±9,66 vs 45,12±8,75 months, p=0.001). Close to the threshold of statistical significance are the $CD_4$ nadir (97,33±65,6 vs 123,15±43,35 cells/$mm^3$, p=0.058) and duration of use of d–drugs (22,5±31,94 vs 12,24±8,6 months, p=0.057). Odds ratio (OR) and relative risk (RR) increase with age. ROC analysis for the study group establishes a threshold difference of 29 years (sensitivity 50%, specificity 80%). Conclusions: higher age and advanced immunosupression are the most important risk factors for developing symptomatic peripheral neuropathy in Romanian HIV infected patients; taking into account the small number of cases studied, although not statistically significant, it should be noted the $CD_4$ nadir and the length of d-drug use.

***KEYWORDS:*** *HIV, risk factors, peripheral neuropathy*

## Introduction

Neurological sufferings associated with HIV infection, especially those involving the central nervous system, are well known to the medical staff. Peripheral neuropathies are the most common neurological manifestations occurring in HIV-infected patients, sometime rising diagnostic or therapeutic problems to the clinicians

In Romania, for the last 20 years knowledge about HIV/AIDS infections have become largely available to doctors, however so far no consistent data are available on the peripheral nervous system sufferings associated to HIV infections among Romanian patients.

The present study aims of detecting risk factors for symptomatic peripheral neuropathy in a group of HIV infected Romanian patients (Px).

## Material and methods

This is a retrospective study based on data colected from the HIV infected Px admitted in the Infectious Diseases Department (Hospital no. 3 Craiova) between january 1990 – january 2009. All HIV infected individuals diagnosed with symptomatic peripheral neuropaties (N=26, 7,44% from all the HIV infected Px known with neurological, mental or behavioral sufferings) have been selected; the control group (C) consist of 40 Px (7,31% from the remaining HIV infected persons) (Fig.1.).

All cases of peripheral neuropathy have been confirmed by the neurologist.

For both groups the following data have been compared: age, height, HIV mode of transmission, number of Px who developed AIDS, average and nadir of the CD4 count during monitoring, mean of HIV viral load, median duration of ART, use and duration of d-drugs (ddI - didanosine, ddC - dideoxicitidine, d4T - stavudine), presence of certain coinfections and conditions (hepatitis B, CMV, toxoplasmosis, tuberculosis, diabetes, concomitant ethanol abuse).

Statistical analysis: differences between groups are based on $Chi^2$ test (two tailed, with Yates correction – calculated using EPI6 program) who estimated the odd ratio (OR) and relative risk (RR), respectively unpaired t test (online Graphpad Quickcalcs) for comparing averages and standard deviations between the two groups, statistical significance being considered for p-value less than 0.05. To detect the optimal level of differentiation (sensitivity vs


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specificity) between the two groups ROC analysis has been used (Receiver Operator Curve, calculated with MedCalc 10.1.3.0 statistical program) to calculate the area under the curve (AUC, required level > 0 5) and the p coefficient (significant if less than 0.05).

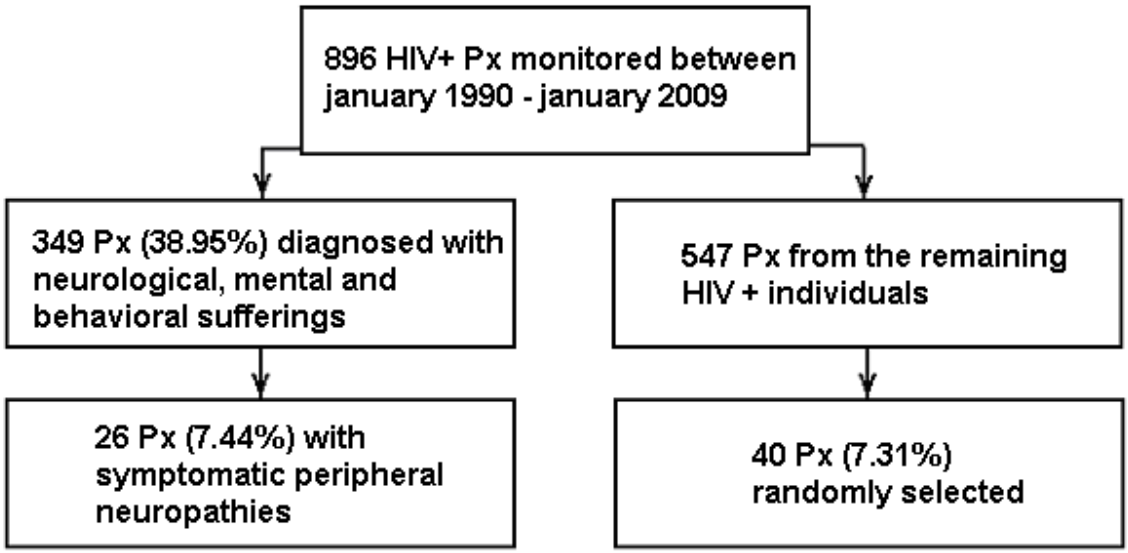


***Fig.1. Selection of the Px (group N and C)***

## Results

The demographic characteristics of the patients are: age – 31.54 ± 14.64 years (group N) vs 23.9 ± 12.03 years (group C), p=0.024 (t test); gender ratio (male/female) – 11/15 (group N) vs 23/17 (group C), p=NS ($Chi^2$); provenance (urban/rural) – 10/16 (group N) vs 24/16 (group C), p=NS ($Chi^2$).

The height of the Px was 1.69 ± 0.085 m. (group N), respectively 1.66 ± 0.11 m. (group C), with no statistical difference between the two groups.

***Table 1. Elements of comparison regarding HIV infections and ART***

| | **Group N (26 Px)** | **Group C (40 Px)** | **p-value** |
|---|---|---|---|
| HIV clinical staging (CDC)<br>A vs B vs C (no. of Px) | 0 / 12 / 14 | 0 / 11 / 29 | NS ($Chi^2$)<br>B vs C stage |
| HIV immunological staging (CDC)<br>1 vs 2 vs 3 (no. of Px) | 1 / 6 / 19 | 1 / 12 / 27 | NS ($Chi^2$)<br>2 vs 3 stage |
| Average $CD_4$ count ± SD (cells/$mm^3$)<br>**median no. of determinations/Px= 5* | 290.17 ± 201.4 | 339.83 ± 265.51 | NS (t test) |
| Nadir $CD_4$ count± SD (cells/$mm^3$) | 97.33 ± 65.6 | 123.15 ± 43.35 | NS (t test)<br>**(0.058)** |
| Average HIV viral load ± SD (copies./$mm^3$)<br>**average no. of determinations/Px = 3* | 157306.6<br>± 68013.9 | 124660.92<br>± 115197.05 | NS (t test) |
| Average lenght of ART ± SD (months)<br>*all Px followed ART | 37.2 ± 9.66 | 45.12 ± 8.75 | **0.001** (t test) |
| Past or present usage of d-drugs (no. of Px) | 23 vs 3 | 28 vs 12 | NS ($Chi^2$) |
| Association of d-drugs (no. of Px) | 13 din 26 | 27 din 40 | NS ($Chi^2$) |
| Average lenght of d-drugs usage ± SD (months) | 22.5 ± 31.94 | 12.24 ± 8.60 | NS (t test)<br>**(0.057)** |

The average time of clinical monitoring was 5.31 ± 3.07 years (group N) vs 7.75 ± 5.4 years (group C), p=0.043 (t test). Regarding the acquisition of the virus, for the group N we have counted 13 Px with parenterally HIV transmission and 13 Px with viral transfer through sexual route, while for the group C we have recorded 28 parenterally transmision and only 8 sexual acquisition of HIV (4 cases had unknown mode of infection). Considering the parenteral vs sexual mode of infections, there was a statistical significant difference between the two groups (p=0.044, Chi2). AIDS has been diagnosed in 21 Px from group N vs 29 Px from group C (p=NS, $Chi^2$). Other elements of comparison (regarding HIV infections and ART) and the significance of the differences between the two groups are shown in Table 1

Table 2 highlights the differences between groups regarding the presence of certain coinfections and associated medical conditions.

***Table 2. Comparison between groups regarding the presence of certain coinfections and associated conditions***

| | **Group N (26 Px)** | **Group C (40 Px)** | **p-value** |
|---|---|---|---|
| HBsAg presence (no. of Px) | 3 vs 23 | 5 vs 35 | NS ($Chi^2$) |
| Presence of antibodies agains CMV (no. of Px) | 5 vs 21 | 4 vs 36 | NS ($Chi^2$) |
| Presence of antibodies against *T. gondii* (no. of. Px) | 12 vs 14 | 11 vs 29 | NS ($Chi^2$) |
| History of tuberculosis (no. of Px) | 9 vs 17 | 12 vs 28 | NS ($Chi^2$) |
| History of diabetes mellitus (no. of Px) | 2 vs 24 | 1 vs 39 | NS ($Chi^2$) |
| Alcohol abuse (no. of Px) | 10 vs 16 | 10 vs 30 | NS ($Chi^2$) |

Differences regarding the chance of detection (OR) and the relative risks (RR) for symptomatic peripheral neuropathy based on the age of the subjects are shown in Table 3; the level of comparison is represented by the first row of the table (patients aged 60).

In Fig.2 is shown the results of the ROC analysis for the differentiation between Px with or without peripheral neuropathy depending on their age (AUC=0.683, p-value=0.0081); 29 years of age represents the optimum point of differentiation between those subjects (sensitivity = 50%, specificity = 80%).

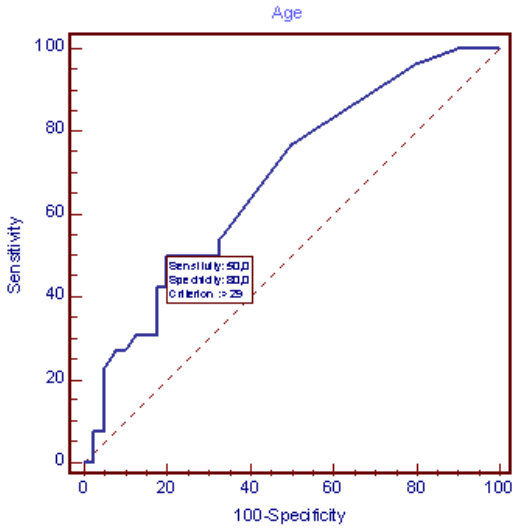


***Fig.2. ROC analysis for the differentiation between Px with or without peripheral neuropathy depending on their age***

***Table 3. OR and RR for developing symptomatic peripheral neuropathy depending on the age gap***

| **Age** | **Disease +** | **Disease -** | **OR ($Chi^2$)** | **RR ($Chi^2$)** | **p-value** |
|---|---|---|---|---|---|
| 60 | 25 | 1 | - | - | - |
| 55 | 24 | 2 | 2.8 | 1.04 | NS |
| 50 | 23 | 3 | 3.26 | 1.09 | NS |
| 45 | 20 | 6 | 7.5 | 1.25 | NS |
| 40 | 19 | 7 | 9.21 | 1.32 | **0.054** |
| 35 | 18 | 8 | 11.11 | 1.39 | **0.027** |
| 30 | 15 | 11 | 18.33 | 1.67 | **0.003** |
| 25 | 13 | 13 | 25 | 1.92 | **0.0005** |
| 20 | 12 | 14 | 29.17 | 2.08 | **0.0002** |


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## Discussion

According to expert studies the prevalence of HIV-associated peripheral neuropathy varies widely between 1.2 and 69.4 %[1, 2]. The incidence of this sufferings dropped down from 27 cases / 100 Px / year prior to highly active antiretroviral therapy (HAART) to 6 cases / 100 Px / year currently; however, when AIDS is diagnosed, the incidence reaches 30% (based on clinical observations), while post-mortem studies reveals an incidence of almost 100% [3, 4]. Our data shows that only 26 HIV infected Px from a total of 896 subjects have been diagnosed with symptomatic peripheral neuropathy - 2,6% or 0.16 cases / 100 Px / year – much under the level revealed by the international data.

The medical literature describes several risk factors for developping peripheral neuropathy in HIV-positive patients: advanced age, chronic alcoholism, presence of other concomitant severe sufferings or AIDS stage, anemia, low CD4 count (or low CD4 nadir), high viral load, antiretroviral therapy used in combination (especially the nucleoside reverse transcriptase inhibitors), or concomitant use of anti-tuberculosis drugs [1, 5, 6, 7]. Many of this factors have been monitored by the present study.

Mitochondria are essential for nerve functioning. They are produced near the root of the nerve and then distributed along the nerve with its elongation [8]. Longer nerve means longer distances between mitochondria, so tall persons are more prone to developing HIV associated peripheral neuropathy [5]. Mitochondria DNA damage due to aging or abnormal oxidative metabolism is associated with nerve sufferings [9]. This study revealed no differences in the height of the patients (seen as a surrogate marker for nerve leg length) of both N and C groups. It is worth mentioning that in parenterally HIV-infected Px (for which the HIV infection has been diagnosed in childhood) they have recently completed the period of body growth, which means that with the increase in length new (fully functional) mitochondria attached to the axons were produced, balancing the old one.

There was a statistically significant difference regarding the age of the subjects and half of the cases have been recorded after 2006, in older Px infected through sexual route. They are also responsible for the differences seen in the duration of monitoring and ART. Given the fact that, both in Romanian subjects infected during childhood or adulthood, the F1 subtype of HIV prevails (i.e. there are no differences in the neurovirulence of the HIV strains) [10] directs us to consider the higher age of patients in group N is the most important risk factor for symptomatic peripheral neuropathy in our group of Px. Our data shows that the greater the age gap the higher the odds of developing HIV associated symptomatic peripheral neuropathy.

The CD4 nadir below 200 cells/mmc, lower in group N, close to the point of statistical significance, suggests that HIV itself and/or opportunistic infections (characteristic of advanced stage of immunosuppression) may contribute to the developing of HIV-associated peripheral neuropathy.

Nucleoside reverse transcriptase inhibitors, in particular d-drugs, affect mitochondrial activity. In the analyzed group no differences were found regarding the use of d-drug regimens used for the treatment of HIV, which is explained by the history of ART in Romania (most Px were exposed to d-drugs especially during the bi-therapy period); however the lenght of the d-drugs use is higher among patients diagnosed with peripheral neuropathy, and the difference is close to the point of statistical significance, so if we take into account the small size of the groups, maybe this factor can be retained for further analysis on larger cohots.

## Conclusions

The present study reveals that higher age and advanced immunosupression are the most important risk factors for developing symptomatic peripheral neuropathy in Romanian HIV infected patients; taking into account the small number of cases studied, although not statistically significant, it should be noted the CD4 nadir and the length of d-drug use. Further studies (with a larger number of subjects) are needed to clarify these issues.

### Abbreviations

ART – antiretroviral treatment
AUC – area under the curve
HAART – highly active antiretroviral therapy
NS – not statistically significant
OR – odds ratio
Px – patients
ROC – receiver-operator curve
RR – relative risk
SD – standard deviation

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