

No evidence of relationship between HIV peripheral neuropathy and the presence of hemochromatosis (HFE) gene mutations.

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Abstract

Background: Hemochromatosis (HFE) gene mutations have been associated with a decreased risk of peripheral neuropathy (PN) in HIV+ patients during antiretroviral therapy.

Methods: A case control study was performed. All patients with a diagnosis of PN based on electromiography were studied for the presence of HFE gene mutations.

Results: 57 patients affected by PN were studied. Among them, 36 (63%) had no HFE mutations, 14 (25%) had H63D heterozygosis, 3 (5%) had H63D homozygosis and 4 (7%) had C282Y heterozygosis. Among the 57 control-group patients, 42 (73%) had no HFE mutations, 14 (25%) had H63D heterozygosis, 1 (2%) had H63D homozygosis and 0 had C282Y heterozygosis. At the univariate analysis, being intravenous drug user, earlier year of HIV diagnosis, CDC '93 class C, nadir CD4+ and exposure to D4T appeared to be associated with development of PN, but not the absence of HFE mutations.

Conclusions: Our results did not support the association between HFE mutations and risk of PN.

Background

Peripheral neuropathy (PN) is a frequent complication of HAART containing NRTI. Its pathogenesis was associated with mitochondrial injury and oxidative stress but the actual mechanisms are not fully known. A recent multicentre case-control study (Kallianpur et al., 2006) showed a decreased risk of PN in patients with hemochromatosis (HFE) mutations (C282Y, H63D). However, the number of patients was small, they were treated with a fixed NRTI backbone (D4T+DDI) and diagnosis of PN was not confirmed by electromiography. Thus the clinical applicability of the above observation could be debated.

The objectives of our study were :

-To verify the relationship between HFE mutations and PN

-To assess other factors which may influence the risk of PN

Methods (I)

A case control study was performed. We selected all patients with a diagnosis of PN based on electromiography (i.e., cases) among HIV positive patients attending the Clinic of Infectious and Tropical Diseases of the University of Brescia and studied them for HFE mutations. Patients not suffering from signs or symptoms of PN (controls) were selected from the same Clinic and matched with cases for the following factors: age (± 5 years), gender, alcohol abuse, HCV Ab reactivity, diabetes. The possible influence or other factors which may also cause PN was explored (risk factor for HIV acquisition, year of HIV diagnosis, nadir CD4+, exposure to dideoxynucleoside analogues [DDX such as D4T, DDI or DDC]).

Methods (II)

Lab methods: Both HFE H63D and C282Y analyses were performed by Polymerase Chain Amplification Reaction (PCR) and Denaturing High Performance Liquid Chromatography (DHPCLC) as described by Biasotto et al, 2003.

Statistical analysis: The data were analysed with conditional logistic regression model to account for matched case-control data (Hosmer et al, 1989). Univariate logistic regression model was used to identify variables associated with outcome. Results are expressed as Odds Ratio with their 95% confidence limit. Analyses were performed with STATA (StataCorp, 2006, Stata Statistical Software: release 9.0, College Station, TX, USA).

Results (I) - patient characteristics

Characteristic	Case-group	Control-group
N of patients	57	57
Italian, N (%)	55 (96%)	53(93%)
Male gender, N (%)	47 (82%)	47 (82%)
Mean age (years)	46	44
HCV Ab+, N (%)	35 (61%)	35 (61%)
Alcohol abuse, N (%)	11 (19%)	11 (19%)
Diabetes, N (%)	3 (5%)	3 (5%)

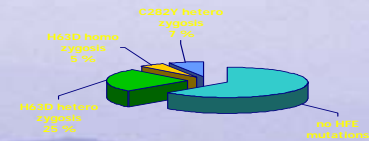
Results (III) - predictors of peripheral neuropathy

In this case-control study, at the univariate analysis, the presence of HFE mutations did not appear to protect from the development of PN while being intravenous drug user, earlier year of HIV diagnosis, CDC '93 class C, lower CD4+ nadir and exposure to D4T appeared to be associated with risk of PN.

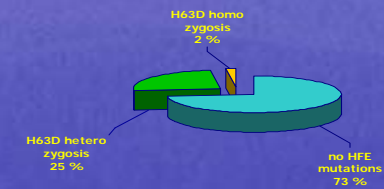
Conclusions

Prevalence of HFE gene mutations in this group of HIV+ patients with a diagnosis of PN confirmed by electromiography was even higher than that found in the Italian general population in the same region (15% in the general population vs. 30% in our population for H63D and 5% vs. 7% for C282Y heterozygosis, respectively). The use of HFE characterization for prediction of PN does not appear to be supported from our data. More studies are necessary to clarify the causative relationship between HFE mutations, iron metabolism and PN.

Results (II) - prevalence of HFE mutations



HFE mutations in the case-group of HIV+ patients with a diagnosis of PN



HFE mutations in the control-group of HIV+ patients without a diagnosis of PN

Tested risk factors for PN	Case-group	Control-group	OR 95% CI	p
Intravenous drug use	35 (61%)	24 (42%)	4.66 (1.34-16.24)	0.015
HIV diagnosis before 1995	35 (61%)	25 (44%)	0.44 (0.19-1.02)	0.056
CDC'93 class C	28 (49%)	15 (26%)	3.17 (1.26-7.93)	0.014
CD4 nadir mean (SD)	119 (115)	155 (103)	1.00 (0.99-1.00)	0.047
D4T-exposure	35 (61%)	27 (47%)	2.33 (0.94-6.07)	0.082
DDI-exposure	28 (49%)	33 (58%)	0.58 (0.23-1.48)	0.257
DDC-exposure	8 (14%)	11 (19%)	0.63 (0.21-1.91)	0.410
H63D heterozygosis	14 (25%)	14 (25%)	1.06 (0.42-2.7)	0.905
H63D homozygosis	3 (5%)	1 (2%)	3.04 (0.31-29.63)	0.338
C282Y heterozygosis	4 (7%)	0	Not done	Not done