Rigshospitalet, University of Copenhagen

COPENHAGEN CO-MORBIDITY IN HIV INFECTION STUDY

Hematological manifestations in virologically-suppressed people living with HIV*: A substudy to the Copenhagen Comorbidity in HIV Infection (COCOMO) Study*

Delal Akdag[1] BSc; Andreas Dehlbæk Knudsen[1] MD; Rebekka Faber Thudium[1] MD; Ditte Marie Kirkegaard-Klitbo[2] MD; Peter Brown[3] MD DMSc Associate Professor; Shoaib Afzal[4] MD; Børge G. Nordestgaard[4,5] MD DMSc Professor; Jens Lundgren[1,6] MD DMSc Professor, Susanne Dam Nielsen[1] MD DMSc Associate Professor

[1]Viro-immunology Research Unit, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2] Department of Infectious Diseases, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; [3]Department of Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [4]The Copenhagen General Population Study, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; [5]Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [6]CHIP, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Objectives

Data on prevalence and severity of anemia, neutropenia, lymphocytopenia and thrombocytopenia in people living with HIV (PLWH) are inconclusive. We aimed to determine the prevalence of the abovementioned cytopenias in well-tcontrolled PLWH compared to uninfected controls. Furthermore, we determined if HIV is an independent risk factor for the four dependent outcomes of interest in the well-controlled PLWH in the contemporary cART era.

Material and methods

PLWH without detectable viral replication or chronic hepatitis infection were recruited from the Copenhagen Comorbidity in HIV infection (COCOMO) study. Age- and sex-matched uninfected controls were recruited from the Copenhagen General Population Study. Demographic data were collected from uniform questionnaires. Venous blood samples were collected and analyzed using the same laboratory and equipment in the two populations. The four outcomes were defined, according to the Common Terminology Criteria of Adverse Events (CTCAE) version 5.0. Logistic regression analyses were performed to determine the association between HIV infection and the four dependent outcomes of interest, after adjusting for age, sex, ethnicity, smoking status, alcohol and hs-CRP.

Results

796 PLWH and 2388 were included in the study. All PLWH had undetectable viral replication. The majority of PLWH and controls were male (84.1% vs. 85.2%, *p*=.423) of Scandinavian decent (73.3% vs. 89.0%, *p*<.001).

Table 1.

Clinical characteristics	PLWH (n=796)	Uninfected controls (n=2388)	p
Age, median (IQR)	50.2 (43.2 – 57.8)	50.5 (43.4 – 58.5)	.6082
Sex (male), n (%)	669 (84.1%)	2035 (85.2%)	.4233
Ethnicity, n (%)			
• Scandinavian	577 (73.3%)	2033 (89.0%)	<.0001
• Other European	90 (11.4%)	162 (7.1 %)	<.0001
• Other	120 (15.3%)	90 (3.9%)	<.0001
Smoking, n (%)			
• Never	253 (32.8%)	1189 (50.1%)	<.0001
• Current	235 (30.4%)	320 (13.5%)	<.0001
• Former	284 (36.8%)	863 (36.4%)	.8146
Alcohol g/week, median (IQR)	84.0 (24.0 – 168.0)	84.0 (36.0 – 168.0)	.1441
Educational level, n (%)			
• None	90 (12.1%)	88 (7.2%)	<.0001
• Short	81 (10.9%)	90 (7.4%)	<.0001
• Vocational	214 (28.7%)	431 (35.2%)	<.0001
• Medium length	171 (23.0%)	318 (26.0%)	<.0001
• University degree	189 (25.4%)	297 (24.3%)	<.0001
Acute febrile disease during the last four weeks (yes), n (%)	44 (5.9%)	41 (3.4%)	<.0001
hs-CRP mg/L, median (IQR)	1.2 (0.6 – 2.5)	1.0 (0.5 – 1.8)	<.0001
Mode of transmission, n (%)			
• MSM	562 (71.3%)		
• Heterosexual	178 (22.6%)		
• IDU	7 (0.9%)		
• Other	41 (5.2%)		
Current CD4⁺ (cells/µL), median (IQR)	690 (530 – 890)		
CD4⁺ nadir <200 (cells/µL), n (%)	303 (38.8%)		
CD4⁺:CD8⁺ ratio, median (IQR)	0.8 (0.6 – 1.2)		
History of AIDS, yes, n (%)	134 (17.0%)		
Zidovudine, current use, n (%)			
• **Yes**	4 (0.5%)		
• **No**	792 (99.5%)		

Abbreviations: PLWH, People living with HIV; IQR, Interquartile range; MSM, male-to-male sex; IDU, intravenous drug use; cART, combined antiretroviral therapy.

Median age for PLWH and controls was 50.2 (43.2-57.8) vs. 50.5 (43.4-58.5), *p*=.608. Most PLWH (99.2%) were on cART, and the median time since diagnosis was 13.7 years. PLWH had a higher prevalence of anemia (6.9% vs. 3.4%, P<.001), neutropenia (1.3% vs. 0.2%, P<.001) and thrombocytopenia (5.5% vs. 2.7%, P<.001) compared to uninfected controls. There was no difference in prevalence of lymphocytopenia between PLWH and controls (2.4% vs. 1.6%, P=.168). In adjusted multivariable logistic regression analyses, HIV was independently associated with the prevalence of anemia (adjusted odds ratio (aOR) 2.0 [95% CI: 1.4-3.0]), neutropenia (aOR 6.3 [95% CI: 2.0-19.6]) and thrombocytopenia (aOR 2.7 [95% CI: 1.8-4.2]). No association was found between HIV and lymphocytopenia.

Table 2.

Prevalence of cytopenia	PLWH (n= 796)	Uninfected controls (n= 2388)	P
Hemoglobin (mmol/L), median (IQR)	9.1 (8.7 – 9.6)	9.2 (8.7 – 9-6)	.1245
Normal	741 (93.1%)	2307 (96.6%)	-
Anemia	55 (6.9%)	81 (3.4%)	<.0001
Neutrophil granulocytes (x10⁹ cells/L), median (IQR)	3.6 (2.8 – 4.5)	3.9 (3.2 – 4.8)	<.0001
Normal	786 (98.7%)	2383 (99.8%)	-
Neutropenia	10 (1.3%)	5 (0.2%)	<.0002
Lymphocytes (x10⁹ cells/L), median (IQR)	2.2 (1.8 – 2.7)	2.0 (1.7 – 2.5)	<.0001
Normal	777 (97.6%)	2349 (98.4%)	-
Lymphocytopenia	19 (2.4%)	39 (1.6%)	.1687
Thrombocytes (x10⁹ cells/L), median (IQR)	226.5 (194.0 – 262.5)	240.0 (206.0 – 279.5)	<.0001
Normal	752 (94.5%)	2324 (97.3%)	-
Thrombocytopenia	44 (5.5%)	64 (2.7%)	.0001

Figure 1.

	Anemia		Neutropenia		Lymphocytopenia		Thrombocytopenia	
Model 1	aOR [95% CI]	p	aOR [95% CI]	p	aOR [95% CI]	P	aOR [95% CI]	p
HIV, yes versus no	2.0 [1.4 – 3.0]	.0003	6.3 [2.0 – 19.6]	.0014	1.6 [0.9 – 2.9]	.1270	2.7 [1.8 – 4.2]	<.0001
Age, per decade	1.5 [1.2 – 1.7]	<.0001	0.8 [0.5 – 1.3]	.3397	1.6 [1.3 – 2.1]	<.0001	1.4 [1.2 – 1.7]	.0003
Sex, male versus female	1.2 [0.7 – 2.0]	.5658	1.3 [0.3 – 6.1]	.7623	0.9 [0.4 -1.9]	.7192	1.2 [0.7 – 2.3]	.4983
Model 2								
Acute febrile disease during the last four weeks, yes versus no	1.3 [0.5 – 3.3]	.6451	<0.001 [<0.001 - >999.9]	.9760	3.3 [1.1 – 10.0]	.0361	0.6 [0.1 – 2.4]	0.4336
Inflammation, hsCRP	1.0 [1.0 – 1.1]	.0022	1.0 [0.8 – 1.2]	.8525	1.0 [1.0 – 1.1]	.0581	1.0 [1.0 – 1.1]	.5245

Model 1: adjusting for HIV infection, age, sex, ethnicity, smoking status and alcohol intake.
Model 2: adjusting for hsCRP and 'acute febrile disease during the last four weeks' in addition to the variables from model 1.
aOR: adjusted odds ratios.
[95% CI]: 95% confidence intervals.

Conclusion

Even in PLWH with successful viral suppression and absence of chronic hepatitis infection, HIV infection is independently associated with higher prevalence of anemia, neutropenia and thrombocytopenia. Although cytopenias are relatively rare, HIV remains a risk factor for cytopenias in the contemporary cART era and requires ongoing attention and monitoring.