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Behavioral Sciences

Psychoneuroimmunologic Correlates in a Group of Men who Have Sex with Men with Risky Sexual Behaviors

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ABSTRACT – This work aims to know what correlations can be found among psychological, neuropsychological, neurobiological, and immunological measures in a group of men who have sex with men negative for anti-HIV-1/2 antibodies which have sexual risk behaviors. Statistically significant correlations were found among certain behavioral, emotional, personality, neurobiological, and immunological variables. The circuit of interactions among depression, stress, neuroticism, and conscientiousness stands out, which could indirectly explain risky sexual behavior. In summary, there is a relationship between personality characteristics, mood disorders, risk behaviors, and an activated T cell profile.

KEYWORDS: psychoneuroimmunology, HIV, mood disorders, risky sexual behavior, personality traits

Os Correlatos Psiconeuroimunológicos em um Grupo de Homens que Fazem Sexo com Homens com Comportamentos Sexuais de Risco

RESUMO – O objetivo deste trabalho é conhecer as correlações que podem ser encontradas entre as medidas psicológicas, neuropsicológicas, neurobiológicas e imunológicas em um grupo de homens que fazem sexo com homens com HIV-1/2 anti-corpos-negativos que se envolvem em comportamentos sexuais de risco. Foram encontradas correlações estatisticamente significativas entre certas variáveis comportamentais, emocionais, de personalidade, neurobiológicas e imunológicas. Destaca-se o circuito de interações entre depressão, estresse, neuroticismo e responsabilidade, que poderia explicar indiretamente o comportamento sexual de risco. Em resumo, há uma relação entre características de personalidade, distúrbios de humor, comportamentos de risco e um perfil de célula T ativado.

PALAVRAS-CHAVE: psiconeuroimunologia, HIV, transtornos de humor, comportamento sexual de risco, traços de personalidade

HIV risk is 26 times higher among gay men and other men who have sex with men (MSM) compared to the general population, and they account for 17% of new HIV infections during 2018 worldwide (40% in Latin America) (UNAIDS, 2019). There is evidence of an epidemic increase of HIV in MSM, although in other populations it is stable or decreasing (Beyrer et al., 2013). Sexual risk behavior is an important factor associated with increased HIV risk in MSM. Some behaviors have been identified as risk factors for contracting HIV, such as men reporting four or more male sexual partners in six months, unprotected receptive anal intercourse with any HIV-positive partner, and unprotected insertive anal intercourse with HIV-positive partners (Hoff et al., 2012; Koblin et al., 2006). Other HIV-risk sexual behaviors include sex in high-risk settings (such as saunas, bathhouses, or clubs) or while under the influence of alcohol

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or other drugs, especially hallucinogens (Drumright et al., 2006; Shoptaw & Reback, 2007).

The study of MSM often focuses on biological or behavioral aspects separately, and research on psychoneuroimmunological aspects is less frequent. HIV psychoneuroimmunology aims to learn how psychological, neurobiological, and immunological factors relate to the acquisition of HIV infection and disease progression (Kemeny, 1994). In general, HIV research has focused primarily on viral pathogenesis (Marmor et al., 2006), and there is a paucity of interdisciplinary studies between psychology, neuroscience, and immunology. In addition, most research has focused on the assessment of HIV-positive MSM (Vanable et al., 2012).

It is interesting to study both psychological (behavioral, emotional and personality) and biological factors (neurotransmitters, hormones and cellular and molecular factors related to the immune response) associated with the risk of acquiring HIV in key populations, such as MSM, in order to improve basic science prevention programs, as well as social and behavioral interventions. This study aims to learn what correlations can be found among psychological, neuropsychological, neurobiological, and immunological measures in a group of MSM, negative for anti-HIV-1/2 antibodies, who engage in risky sexual behaviors. These correlations may guide interdisciplinary research and highlight the complex mind-body interactions in the study of immune system functioning from an integrative perspective.

METHOD

Type of Study, Participants and Data Collection

A cross-sectional study was conducted with a non-probabilistic sample of 30 MSM, from a reference population of 115,021 MSM in the city of Medellín. All participants were over 18 years of age and voluntarily agreed to be part of a project to study natural resistance to HIV infection. The inclusion of participants was carried out using hard-to-reach population sampling methods (snowball sampling, site sampling, and solicitation through flyers and social media [Facebook® and Grindr®]). Thirty MSM were included who had risky sexual behaviors, such as inconsistent use of a condom with regular and casual partners, multiple sexual partners in the past three months, and history of sexually transmitted infections (STIs). Sociodemographic data were collected using a structured survey and in-depth interviews.

HIV Testing

Participants were tested for anti-HIV1/2 antibodies using a third-generation rapid test (SD HIV-1/2 3.0 Bio Line, Abbot®; sensitivity: 100%; specificity: 99.8%). All included individuals tested negative for anti-HIV-1/2 antibodies.

Immunological Parameters Identification

Phenotypic analysis of peripheral blood mononuclear cells (PBMC) was performed by direct labeling of fresh peripheral blood samples. The percentages of CD4+ and CD8+ T cells and the activation levels of basal CD4+ and CD8+ T cells were assessed by flow cytometry using the following monoclonal antibody combinations: anti-CD4-PerCp-Cy5. 5 (clone OKT4, Thermo Fisher Scientific), anti-CD8-eFluor 450 (clone OKT8, Thermo Fisher Scientific), anti-HLA-DR-FITC (clone LN3, Thermo Fisher Scientific), anti-CD69- APC (clone FN50), anti-CD38- PE-Cy7 (clone HIT2, Thermo Fisher Scientific) and fixable viability dye-eFluor 506 (Thermo Fisher Scientific) for 25 minutes at room temperature in the dark. Erythrocytes were subsequently lysed with BD FACS lysate solution (Becton-Dickinson Immunocytometry System, San Jose, CA) according to the manufacturer's instructions. The cells were then incubated with fixation buffer (Thermo Fisher Scientific) for 30 min at 4°C in the dark. After washing, the cells were resuspended in 1X permeabilization solution (Thermo Fisher Scientific) and stained with anti-Ki-67-PE (clone BD, Thermo Fisher Scientific), anti CD3- Alexa eFluor 700 (clone UCHT1, Thermo Fisher Scientific) for 25 minutes at 4°C in the dark. Flow cytometry was performed on the BD LSRFortessa™ Cell Analyzer. At least 100,000 events were analyzed using FlowJo version 10.5.3 (FlowJo, LLC, Oregon, USA). The plasma sample was obtained by collecting whole blood in commercially available EDTA-treated tubes. Plasma was separated by centrifugation of the blood at 380xg for 10 minutes. For each plasma sample, cytokine concentrations (TNFα, IL-1, IL-6, IL-8, IL-10, IL-12) were measured on a BD LSRFortessa™ cell analyzer using a cytometric bead array (BD) cytokine kit according to the manufacturer's instructions. Results were analyzed with FlowJo version 10.5.3 (FlowJo, LLC, Oregon, USA).

Neurobiological Measures

The presence of cortisol, serotonin and catecholamine (adrenaline, noradrenaline and dopamine) was determined in plasma and serum samples by radioimmunoassay of each individual in a reference laboratory, Prolab-Synlab of Medellin (Colombia).

Psychological and Neuropsychological Measures

A clinical psychologist assessed anxiety, depression and stress using the Beck Anxiety Inventory (Beck & Steer, 1993), the Beck Depression Inventory (Beck et al., 1996) and the Stress Rating Scale (Fernandez & Mielgo, 2001), respectively. The NEO-FFI inventory (Costa & McCrae, 1999) was used to obtain the personality profile. A clinical neuropsychologist applied a neuropsychological battery, Neuropsi (Ostrosky et al., 2012), to assess executive functioning, memory and attention.

Ethical Considerations

All individuals signed an informed consent approved by the Ethics Committee of the Faculty of Medicine of the Universidad de Antioquia. The study and the informed consent were prepared in accordance with Resolution 8430 of the Colombian Ministry of Health and the Declaration of Helsinki and its subsequent amendments. Consideration was also given to the provisions regarding research included in Law 1090 of 2006.

Data Analysis

Through univariate analysis, absolute and relative frequencies were calculated for qualitative variables, and summary measures for quantitative variables. Statistical correlations were made using Spearman's rank correlation coefficient after verification of non-compliance with the normality assumption by the Shapiro Wilk test. The analysis was performed in SPSS software version 25. P values < .05 were considered significant.

RESULTS

The majority of participants were young single adults (*Me* = 26; *IQR* = 22-29) who identified as male (96.7%). The highest percentage was college students (53.3%). Ninety percent defined their sexual orientation as gay/homosexual and the rest as bisexual. Half (50%) of the men have had a partner with HIV/AIDS and most (60%) did not always use condoms. In the last three months prior to study enrollment, the median number of different sexual partners and unprotected sex was 4 (*IQR* = 2-25) and 6 (*IQR* = 1-10), respectively. Other sociodemographic and sexual behavioral results can be found in Table 1.

Table 2 presents the psychological, neurophysiological and immunological variables of the subjects studied. High percentages can be observed with high levels of neuroticism, extraversion, openness, and with low levels of agreeableness. Anxiety had the highest percentage of high levels, followed by stress. In depression, there was an equal percentage of participants with high levels and normal levels. Most neurotransmitters had normal levels, but norepinephrine and serotonin had some cases with high levels. There were neuropsychological alterations in executive functions, memory and attention in 30 percent of the cases. Plasma levels of cytokines and T cells were similar to those reported in other studies in healthy people.

Among the 45 variables analyzed (three behavioral, three emotional, five personality factors, three neuropsychological, five neurotransmitters, one hormone, six molecular and 19 cellular factors related to the immune response), Table 3 presents those in which statistically significant correlations were found ($p < 0.05$). Since the aim was to detect psychoneuroimmunological associations (i.e., associations between variables in different categories, such as emotion/neurotransmitter or personality/molecular association), correlations between variables in the same categories (e.g., emotion/emotion correlations or cellular/cellular correlations, etc.) were excluded.

DISCUSSION

The risk of acquiring HIV is a combination of biological and psychological conditions. Sexual risk behavior is a crucial factor associated with increased HIV in MSM, so behavioral, emotional, and personality correlates are a starting point for analyzing the remaining ones. In this study, the three sexual risk behavior variables were correlated with cellular/molecular factors and emotions. It is not easy to find an explanation to make sense of an association between a molecule and complex sexual behavior. However, when an additional variable is introduced between them, such as an emotion, some explanations can be posited.

The number of sexual partners showed a statistically significant correlation with depression. This association has been demonstrated in previous studies through a positive correlation between depressive and anxious symptoms with sexual risk behaviors (Heath et al., 2012; Houston et al., 2012). Furthermore, this association is exacerbated by drug use and specific personality characteristics, such as extraversion, which has been related to having a high number of sexual partners (Schmitt, 2004), sexual variety seeking (Nasrollahi et al., 2011), and substance use (Atherton et al., 2014).

Table 1
Sociodemographic and sexual behavior characteristics.

	Me (IQR)
Age (years)	26(22-29)
Sexual relations (last three months)	14(5-30)
Different sexual partners (last three months)	4(2-25)
Unprotected sexual intercourse (last three months)	6(1-10)
	***n* (%)**
Schooling	
Postgraduate	1(3.3)
Undergraduate	16(53.3)
Baccalaureate	4(13.3)
Technical	4(13.3)
Technological	5(16.7)
Marital Status	
Single	28(93.3)
Unmarried	2(6.7)
Gender Identity	
Male	29(96.7)
Queer	1(3.3)
Sexual orientation	
Gay/Homosexual	27(90)
Bisexual	3(10)
Have you had a partner with HIV/AIDS?	
Yes	15(50)
No	15(50)
Do you use condoms with your casual partners?	
Always	12(40)
Sometimes	16(53.3)
Never	2(6.7)
Do you use hallucinogens during sex?	
Yes	19(63.3)
No	11(36.7)
Have you ever had STIs?	
Yes	16(53.3)
No	14(46.7)
Casual sex in saunas, bathhouses or clubs?	
Yes	14(46.7)
No	16(53.3)
Transactional sex?	
Yes	1(3.3)
No	29(96.7)

Table 2
Levels of psychological, neuropsychological, neurophysiological and immunological variables.

	Low	Normal	High	NA*
Personality				
Neuroticism	16.7%	43.3%	36.7%	3.3%
Extraversion	20%	30%	46.7%	3.3%
Openness to experience	0%	40%	60%	
Agreeableness	53.3%	36%	6.7%	3.3%
Conscientiousness	7%	76.7%	13%	3.3%
Mood				
Depression		60%	30%	10%
Anxiety		33.3%	66.7%	
Stress		46.7%	50%	3.3%
Neurotransmitters				
Tryptophan		93.3%		6.7%
Adrenaline		83.3%		16.7%
Noradrenaline		63.3%	20%	16.7%
Dopamine		83.3%		16.7%
Serotonin	3.3%	80%	13.3%	
Hormone				
Cortisol		96.7%		3.3%
Neuropsychological				
Executive functioning	30%	70%		
Memory	36.7%	63.3%		
Attention	36.7%	63.3%		
Immunologicals		**Me (IQR)**		
IL-1b (pg/mL)		1.69 (.86-3.01)		
IL-6 (pg/mL)		1.05 (.57-2.50)		
IL-8 (pg/mL)		6.00 (5.04-8.50)		
IL-10 (pg/mL)		.63 (.23-1.62)		
IL-12 (pg/mL)		.42 (.21-1.20)		
TNFa (pg/mL)		1.34 (.53-2.72)		
%CD3**		67.90 (58.80-72.73)		
%CD4**		51.70 (41.35-59.00)		
%CD8**		31.70 (26.58-38.03)		
%CD4HLADR+CD38+**		3.11 (1.84-4.93)		
%CD4HALDR-CD38-**		46.35 (36.80-55.83)		
%CD4CD69+**		.32 (.12-0.83)		
%CD4Ki67+**		3.90 (2.32-5.77)		
%CD8HLADR+CD38+**		8.42 (5.23-12.70)		
%CD8HALDR-CD38-**		49.00 (32.90-62.53)		
%CD8CD69+**		1.01 (.60-1.56)		
%CD8Ki67+**		2.63 (1.61-4.40)		

*Not available
**Percentage of positive cells of PBMC

Table 3
Spearman's rank correlation coefficient for p-values < 0.05.

		r_s	p
Sexual Relationships	IL8	.41	.02
Sexual partners	Depression	.43	.02
	Memory	-.36	.49
	IL12	-.38	.03
	CD4 HLA DR- CD38+ (% cells)	-.36	.04
Unprotected sex	IL8	.36	,04
Dopamine	Anxiety	-.49	.007
	CD4 HLA DR+CD38+ (% cells)	-.39	.03
	CD8 Ki67+	-.38	.04
Adrenaline	Cortisol	.51	.009
	Openness to experience	-.42	.03
	CD4	.41	.03
Noradrenaline	IL6	-.39	.04
Serotonin	CD4 HLA DR+ CD38+ (% cells)	-.39	.03
	CD4 HLA DR- CD38- (% cells)	.37	.04
	CD8 CD38+	-.43	.01
	CD8 HLA DR- CD38- (% cells)	.42	.02
Cortisol	IL6	-.41	.02
Anxiety	Depression	.64	< .001
	Neuroticism	.70	< .001
	Agreeableness	-.45	.01
	Conscientiousness	-.40	.03
	CD4 CD69+	.42	.02
	CD4 HLA DR- CD38-	-.42	.02
	CD8 HLA DR+ CD38+	.42	.02
	CD8 HLA DR- CD38-	-.45	.01
Depression	Neuroticism	.76	< .001
	Agreeableness	-.48	.01
	Conscientiousness	-.49	.009
	IL8	-.38	.04
Stress	Conscientiousness	-.40	.03
	Executive functioning	-.38	.04
Neuroticism	CD4 CD69+	.37	.04
Extraversion	CD4 HLA DR+ CD38+	-.40	.03
	CD8	.45	.01
	CD8 CD69+	-.42	.02
	CD8 HLA DR+	-.42	.02
Executive functioning	CD3	.44	.01
Memory	CD3	.50	.004

No correlation was found between personality traits and sexual behavior, but a positive correlation was found between neuroticism and depression. Depression was negatively correlated with responsibility, and this personality trait was also negatively correlated with stress. So higher levels of depression and stress are associated with lower levels of responsibility and self-care. People with low responsibility have difficulties with impulse control (Atherton et al., 2014), lack of self-control, and health-related problems (Bogg & Roberts, 2013). There is a circuit of interactions between depression, stress, neuroticism and responsibility, which could indirectly explain risky sexual behavior in some individuals.

It is known that mental health, behavior and the immune system are closely related. Cytokines can modulate neurotransmitter metabolism, which, in turn, has been correlated with the development of depression and fatigue (Miller, 2010). In this study, IL-6 and other pro-inflammatory cytokines were not associated with personality traits. However, high neuroticism and low responsibility have been reported to be associated with high levels of this cytokine (Sutin et al., 2010). Furthermore, using a longitudinal design with path analysis, depression was shown to cause an increase in IL-6 in healthy individuals through the HPA axis and the autonomic nervous system (Stewart et al., 2009). Depression and IL-6 were not associated here, but there was a negative correlation between depression and IL-8. This pattern was reported in depressed women, in whom increased IL-8 was associated with decreased severity of depression (Kruse et al., 2020).

Negatively associated with depression, IL-8 was positively correlated with sexual intercourse and unprotected sex. IL-8 is a pro-inflammatory cytokine that attracts immune cells to an infectious focus, and its positive correlation with risky sexual behaviors could be explained by the significant likelihood of challenging the immune system by exposure to pathogens and different types of microbiota through unprotected sexual interactions. This assumption is consistent with the high prevalence of STI history (53.3%) in the subjects studied. Although no evidence was found in the literature for a direct correlation between IL-8 and HIV risk, there is a clear relationship between sexual risk behaviors, STIs, and inflammatory profiles, all of which contribute to a significant risk of HIV acquisition (Kaul et al., 2015; Passmore et al., 2016).

The connection and interaction between the nervous and immune systems are complex and mediated by neurotransmitters, cytokines and cells (Steinman, 2004; Wu et al., 2019). Dopamine is heavily implicated in immune function (Basu & Dasgupta, 2000), as it inhibits proliferation and cytotoxicity of human CD4+ and CD8+ T cells (Saha et al., 2001) and suppresses NK cell proliferation (Mikulak et al., 2014). Serotonin (5-HT) also plays a role in the immune system as it has been shown that various types of immune

cells can produce, store and respond to serotonin (Wu et al., 2019). In fact, there is increasing evidence of a possible connection between serotonin, T cells and mood disorders (Wu et al., 2019).

However, it is still not understood how this interaction occurs and how serotonin influences the functions of T cells and other immune cells. Some studies suggest a stimulatory role of serotonin on T cells, signaling through some specific receptors that enhance T cell activity (León-Ponte et al., 2007). In turn, there is evidence of its inhibitory function (Schneider et al., 2004), such as inhibition of calcineurin-induced T-cell activation (De la Vega, 2005). In the present study, dopamine and serotonin were negatively correlated with CD4+ and CD8+ T cell activation.

On the other hand, a positive correlation of adrenaline with CD4+ T cells and cortisol was found. In seropositive patients, adrenaline induces a mobilization of T cells (Søndergaard et al., 2000). In contrast, noradrenaline and cortisol were negatively associated with IL-6. Both noradrenaline, cortisol and IL-6 are produced in response to acute stress (Koelsch et al., 2016). However, in this study, no correlation was found between the psychometric measure of stress and norepinephrine, IL-6, or cortisol. Anxiety had strong positive correlations with depression and neuroticism. In addition, anxiety and neuroticism showed a positive correlation with CD4+ and CD8+ T-cell activation profile.

In the context of HIV, T-cell hyperactivation has a significant impact. In people living with HIV, T-cell hyperactivation is associated with poor prognosis and rapid progression to AIDS (Carbone et al., 2000; Resino et al., 2006). In addition, anxiety and depressive symptoms are associated with low CD4+ T-cell levels in people on antiretroviral therapy (Agus et al., 2019). Moreover, a low T-cell activation profile is associated as a protective factor for acquiring HIV in HIV-exposed individuals (Koning et al., 2005) and correlates with viral control (Gonzalez et al., 2016; Hua et al., 2014).

Anxiety also presented a negative correlation with responsibility. Conscientious individuals tend to be less anxious (Kaplan et al., 2015), and the higher the levels of responsibility, the lower the pursuit of sexual variety (Nasrollahi et al., 2011). Moreover, the lower the level of this trait, the greater the likelihood that individuals will engage in risky sexual practices and other risky behaviors (Trobst et al., 2002). Here is another circuit of interactions between emotional, behavioral, and biological conditions correlated with the risk of HIV acquisition and progression.

Neuropsychological variables of executive functioning and memory were positively correlated with CD3+ cells. Molecular neuroscience has presented evidence that T cells contribute to the functioning (pro-cognitive properties) of learning and memory (Kipnis et al., 2012). Neuroticism and extraversion were also correlated with CD4 and CD8 T cells. No other personality traits were associated with immunological factors. As noted, these personality traits have shown consistent patterns of risk behavior. Along with liability, these traits appear to contain a number of emotional, cognitive, hormonal, cellular, and molecular correlates that, under certain social conditions, predispose people to engage in sexual risk behavior for HIV. People who are at least 1 standard deviation above the mean for neuroticism are eight to ten times more likely to have unprotected sex than people who are at least 1 standard deviation below the mean (Hoyle et al., 2000).

Certainly, the interpretation of the correlations was a narrative attempt rather than an explanation. In an overall view, it is desired to emphasize that there appears to be a relationship between personality traits and mood disorders with sexual risk behaviors and, at the same time, with an activated T-cell profile. All of these have been independently associated with HIV risk, but here we posit an interaction between them, and we highlight the possible connection of an activated immune profile and emotional problems, which is evident in another context - even in HIV progression, but it is the sprue in the context of HIV risk (Figure 1).

This study has limitations. It is a cross-sectional study, so it is impossible to establish the precise mechanisms that adequately integrate the interaction between behavior, emotion, personality, neurobiology and immunology into a coherent system of causes and effects. It is well known that correlational analysis must be done on large samples, and this is a limitation of the study. However, it is not easy to access men with sexual risk behaviors, possibly exposed to HIV, but who remain HIV-negative. In addition, the

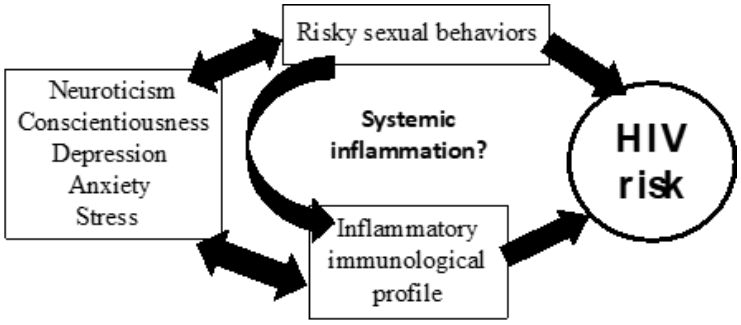

Figure 1. Suggested model of interaction between personality, emotional, behavioral and immunological variables associated with HIV risk.

interdisciplinary work and the high number of measurement instruments and variables implied a high investment of time for each participant.

Concluding, it can be affirmed that there are statistically significant correlations between certain behavioral, emotional, personality, neurobiological and immunological variables in a group of HIV-negative MSM with sexual risk behaviors. It highlights the circuit of interactions between depression, stress, neuroticism and responsibility, which could indirectly explain some sexual risk behaviors. Simultaneously, these emotional conditions are correlated with pro-inflammatory and T-cell activation profiles, which are associated with a significant risk of HIV acquisition. In HIV prevention, knowing these correlations is very important to help build more integrated prevention programs. Establishing a clear understanding of the associations between molecular and cellular factors and behavioral, emotional and personality variables is complex. In order to understand them, a more developed theoretical framework is required to explain the interactions between the nervous system and the immune system and such a framework is under construction. All these results contribute to its development.

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