Psychiatria Danubina, 2016; Vol. 28, Suppl. 1, pp 179-182 *Conference paper*

DEPRESSION, GENDER AND CELLULAR IMMUNITY: INFLUENCE OF GENDER AND SEVERITY OF DEPRESSION ON THE CELLULAR IMMUNITY

Manon Fagniart, Christine Reynaert, Denis Jacques, Bries Lepièce & Nicolas Zdanowicz

Université Catholique de Louvain, Psychosomatics Unit, Mont-Godinne University Hospital, Yvoir, Belgium

SUMMARY

***Background**: Exposure to stress modifies the humoral and cellular immunity by the activation of the hypothalamic-pituitary-adrenal axis. On one hand, this psycho-immunological theory allows the analyse of links between immunity and depression. On the other hand, the correlation between the immune response, the clinical expression in major depressive disorder (MDD) and the gender was proven. Our analysis evaluates the influence of the gender and the level of depression severity on the cellular immune response associated with it.*

***Subjects and method**: 549 patients with MDD were enrolled in an open-ended survey. In addition to a socio-demographic questionnaire, they completed the Beck Depression Scale (BDS). Flow cytometry was used to assess lymphocyte subsets.*

Results**: On average, the intensity of the depression (ID) among women is higher by 2.9 points (t=2.379*). In terms of immunity, there are correlations between this ID and absolute values of CD3 (r=-0.127), CD4 (r=-0.189***), CD8 (r=0.089*) and CD16 and 56 (r=0.129*). In terms of gender, there are significant differences for the percentage of total lymphocytes (m=37.84, w=35.59; t=2.646***), CD3 (m=2.08, w=1.9; t=2.676*), CD4 (m=1.44, w=1.3; t =2.522*), CD8 (m=0.62, w=0.57; t=2.182*). A linear regression model including both variables supports the existence of these differences in the percentage of total lymphocytes (Adjusted R2=0.025***) and CD8 (Adjusted R2=0.012*).*

***Conclusions:** If the link between depression and the cellular immune response is a known fact, our study proves that women have a stronger immune response than men in terms of percentage of total lymphocytes mobilized and cytotoxic lymphocytes. The volume of natural killer lymphocytes is independent of the gender but connected to the ID. Based on those results, psycho-immunological theories could potentially be rethought in the light of immunity being at least partially dependent of the gender.*

***Key words:** immunity – gender – depression*

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INTRODUCTION

The number of studies performed on the link between depression and immunity is large. Indeed, depression is characterized by immunosuppression and concomitant immunoactivation (Blume 2010). The immunosuppression caused by stress is characterized by a decrease in the proliferation of innate and humoral immune cells and more precisely a contraction of the level of cytotoxic natural killer (NK) cells and of anti-inflammatory cytokines (Eyre et al. 2014). The immunoactivation is defined by an inflammatory condition characterized by an increase of the number of pro-inflammatory cytokines such as IL-6, TNF alpha and CRP (Blume et al. 2010, Eyre et al. 2014). Indeed several arguments are in favor of an inflammatory component in the pathophysiology of MDD: Leonard & Maes (2011) are highlighting the fact that inflammation promotes the expression of the enzyme IDO (Indoleamine-pyrrole 2,3-dioxygenase), itself causing a decrease of serotonin and the production of neurotoxic metabolites (catabolite of tryptophan, TRYCATs) which are depressogenic and anxiogenic. The level of serotonin influences the function of NK cells, macrophages and T cells among others. It also decreases the activation of CD4 + T cells. Serotonin plays a role in T-cell proliferation (via 5-HT1aR). (Blume et al. 2010, Eyre et al. 2014, Li et al. 2009, Andrew & Miller 2010). The resistance to glucocorticoids is another mechanism that may explain the immune deregulation in depression. Usually, glucocorticoids have an anti-inflammatory effect but may have a pro-inflammatory effect in some circumstances (Blume et al. 2010, Eyre et al. 2014). Decreased levels of activity of NK cells and of T cell proliferation; increased apoptosis of T cells and increase in the CD4/CD8 ratios have been seen in depression (Eyre et al. 2014, Grosse et al. 2015, Zorilla et al. 2011). Depression is associated with an increased number of activated cytotoxic T cells (CD8+) but a fall in CD4 + levels (Eyre & Baune 2012). Stress hormones have a deleterious effect on immunity with a decrease in NK cells activity, a proliferation of the population of lymphocyte and the production of Ac (antibodies) with a change on the ratio of T-helpers and T-suppressors. CD4 + cells promote antibodies production by B lymphocytes. Stress causes an increase in CD8 + levels while relaxation increases the percentage of CD4 + cells (Marketon & Glaser 2008). Stress causes a reduction of the BDNF (Brain-Derived Neurotrophic Factor) which causes a decrease in neurogenesis via cytokine secretion (Andrew & Miller 2010, Eyre & Baune 2012, Mahar et al. 2013).

There is by far less data and publications on the link between immunity and gender. As statistically women are twice more affected by depression than men, the fact

that gender hormones play a crucial role in depression probability could be a fair assumption. Our study aims to underline that immunity plays a role on this difference.

Women have higher levels of immunoglobulins, as well as a prolonged and stronger immune response compared to men when facing an infection. Nevertheless, women are more likely to develop autoimmune diseases caused by the higher risk of autoreactive antibodies development (Pitychoutis & Papadopoulou-Daifoti 2010, Trigunaite et al. 2015).

Estrogens are associated with a neuroprotective role in neuronal survival (Pitychoutis & Papadopoulou-Daifoti 2010), however, estrogen has an anti-inflammatory or pro-inflammatory role depending on the context in which they are (concentration, environment...). The influence of estrogen on inflammatory pathways is dependent on the context (Straub 2007, Kovats 2015). A unique concept to describe the influence of estrogen on chronic inflammation level is illusionary.

However, the immunosuppressive effect of androgens in known. Testosterone reduces antibodies, cytokines and B and T lymphocytes rates. It inhibits as well the cellular and adaptive immunity by inhabitation of the proliferation of T cells trough the thymus). Finally, testosterone stimulates the production of IL-10 cytokine which is known for its anti-inflammatory effects (Trigunaite et al. 2015).

SUBJECTS AND METHODS

Our study is an open-label trial carried out over 4 years and includes 545 patients hospitalized for a MDD in the Psychosomatic Department of the Cliniques Universitaires de Mont-Godinne, Belgium.

All patients admitted to the Department completed a socio-demographic questionnaire (gender, ethnicity, employment status, marital status), together with a visual analogue scale of the severity of life events in the past year and the Beck Depression Inventory (BDI), made of 21 items.

The BDI is a quantitative scale used to estimate the severity of depressive disorders; it has been validated for adults and adolescents aged at least 13 years and is the most widely-used scale in the adult population (Bouvard & Cottraux 2002).

Routine analysis by flow cytometry measured the various lymphocyte populations identified by the antigenic properties of membrane markers; first they include CD3 which are present on all T cells. There are two subpopulations: helper/suppressor and cytotoxic. Secondly the CD4 which is found on helper or auxiliary T cells. These lymphocytes activate the immune response through the release of cytokines and in liaison with other immune cells. The CD4 cell count is a key measure in monitoring HIV infection; a reduction is an indicator of progression towards immunosuppression. Certain bacterial infections can also cause a long-term reduction in the number of CD4 lymphocytes. Conversely, CD4 lymphocytosis is often observed in autoimmune diseases. Thirdly, CD8 which is a cytotoxic marker. These cells are capable of targeted cell destruction once they have been activated. An increase in CD8 is associated with the rapid progression towards immunosuppression. Levels of CD8 can be reduced in autoimmune diseases. Conversely, CD8 lymphocytosis is an indicator of the activation of the immune system. This increase has been observed in viral infections, graft rejection, chronic fatigue syndrome and certain neutropenia. Fourthly the CD4 /CD8 ratio, evaluating the health of the immune system, for example in the progress of AIDS. Fifthly the CD16 and 56 which are surface markers of NK cells. NK cells are capable of destroying their target in the absence of major histocompatibility complex (MHC). NK cells are non-T cells (CD3). NK cell lymphocytosis is common and usually reflects a mild and transient condition. Finally, CD19 which is a B cell surface protein. These cells produce immunoglobulin. As the overall lymphocyte analysis of patients is normal, and for ease of presentation, we only present relative results.

All statistical tests were performed using SPSS 22.0 parametric methods; Type 1 and 2 errors were taken into account. No post-hoc tests were performed. Correlations were performed using Pearson's R Correlation test. Comparisons of qualitative variables used the chi-square test. Means were compared using Student's t-test. Linear regression was used for quantitative variables, where necessary co-variables were classified in descending order of correlation coefficient. Selected significance levels were $p>0.95$ and $p<0.05$.

RESULTS

Influence of socio-demographic variables on the severity of depression

Age

The sample of depressed patients is aged between 18 and 90 years, with a mean of 48 years (SD: 10). There is a statistically significant correlation between the severity of depression and age ($p=0.000$; $r=-0.172$).

Ethnicity

All subjects are Caucasian.

Domestic situation

The average BDI score for the 276 subjects who are in a relationship is 30 (SD: 13). The average score for the 269 individuals who do not have a partner is of 27 (SD: 13). Student's t-test ($t=2.700$, $p=0.007$) shows that these averages are statistically different.

Employment status

The average BDI score for the 260 subjects who are employed is 30, while for the 285 who are not in work, it is 28. The Student's t-test shows no significant difference ($t=-1.647$; $p=0.100$).

Table 1. Correlation between lymphocyte subsets and severity of depression

		Beck
CD3	r	-0.112
	p	
CD4	r	0.015
	p	
CD8	r	-0.175
	p	
Ratio CD4/CD8	r	0.000
	p	
CD19	r	0.080
	p	
CD16 & 56	r	0.060
	p	

Table 3. Successive linear regressions for influence of gender and intensity of depression on immunity

	Adjusted R^2	p
CD 3	0.007	0.069
CD 4	0.005	0.121
CD 8	0.025	*0.001*
% lymphocytes	0.025	*0.001*

Table 2. Correlation between gender and lymphocyte subset

	Average man	Average woman	t	p	Unlike the standard error
CD 3	1.90977	2.08010	2.476	*0.014*	0.068803
CD 4	1.30990	1.44170	2.522	*0.012*	0.052270
CD 8	0.57241	0.62347	2.229	*0.026*	0.022909
CD 19	0.35478	0.36707	0.562	0.574	0.021873
CD 16 and 56	0.21950	0.18705	1.477	0.143	0.021961
% lymphocytes	35.59	37.54	2.646	*0.008*	0.851

Life events over the past year

There is a correlation between the severity of life events in the past year and the severity of depression ($p<0.000$; $r=0.248$).

Socio-demographic impact

Statistical analyses show that age, gender, domestic situation and life events influence the level of depression. Tests of hypotheses therefore control for these variables.

Hypothesis testing

Hypothesis 1: There is a correlation between gender and severity of depression

The sample consists of 201 men and 344 women; a gender ratio of 0.58.

Average BDI scores are 30 for women and 27 for men and the difference is significant ($t=2.492$; $p=0.013$).

The intensity of depression is higher by 2.9 points ($p=0.018$; $t=2.379$) on average among women.

Hypothesis 2: There is a correlation between immune variables and severity of depression

Table 1 shows that all cell classes are correlated with the severity of depression, with the exception of CD8 and CD19. Linear regression with correlated classes shows that the overall model explains 12.7% (adjusted R^2) of the variance ($p<0.000$).

Hypothesis 3: There is a correlation between immune variables and gender

We made an average comparison using Student's t-test.

Table 2 shows that all lymphocyte subsets are correlated with the gender, with the exception of CD19, CD 16 and CD56.

Hypothesis 4: There is an influence of gender and severity of depression on the immune variables

We performed successive linears regressions to investigate the influence of gender and intensity of depression on different lymphocytes subtypes. We have had significant results for CD8 and total lymphocytes.

Table 3 shows that only CD8 and total lymphocytes are correlated with the gender and severity of depression.

DISCUSSION

Several elements emerge. First, depression is not only more common within the women subgroup, as many studies have underlined, but it is also more severe in women group than in men's one. Secondly, there is a connection between the severity of depression and immunity. Indeed, there is a significant correlation between Beck and CD3, CD4, CD4 / CD8 ratio, CD16 and CD56. Thirdly, regarding the link between gender and immunity, all types of lymphocytes are correlated with gender with the exception of CD19, CD16 and CD56. Fourthly, an overall more intense immune response for women than for men on all subgroups except the CD 16 and CD 56 was recorded. Fifthly, regarding to the cumulative impact of the gender and ID on immunity, only CD8 and total lymphocyte have denoted significant results. Sixthly we can therefore conclude that CD 16

and 56 are independent of the gender but correlated with the ID. Seventhly, the CD8 and the total number of lymphocytes are more specificities of the ID. Finally, CD19 is not related to any of the settings, or the kind or ID.

Based on this, our study confirms and complements the findings of previous analysis and publications and provides new perspectives for the treatment of patients suffering from depression, for prevention strategies will potentially open pathways for additional research on this topic.

CONCLUSION

If the link between depression and the cellular immune response is a known fact, our study proves that women have a stronger immune response than men in terms of percentage of total lymphocytes mobilized and cytotoxic lymphocytes. The volume of NK lymphocytes is independent of the gender but connected to the intensity of depression. Based on those results, psychoimmunological theories could potentially be rethought in the light of immunity being at least partially dependent of the gender.

Acknowledgements: None.

Conflict of interest: None to declare.

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Correspondence:
Manon Fagniart, MSc
Université Catholique de Louvain, Psychosomatics Unit, Mont-Godinne University Hospital
5530 Yvoir. Belgium
E-mail: Manon.fagniart@student.uclouvain.be