Psychiatria Danubina, 2017; Vol. 29, Suppl. 3, pp 274-278 *Conference paper*
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DEPRESSION AND IMMUNITY: A PSYCHOSOMATIC UNIT

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SUMMARY

Background: *The effects of depression on the immune system are well known. Recently, depression as a consequence of an immune disorder has received increased research attention. Here, we test the hypothesis that the depression–immunity association is a buffer zone between external stimuli, defence mechanisms, and intrinsic determinants.*

Subjects and methods: *Five hundred and forty-nine patients presenting with a major depressive episode completed the Beck Depression Inventory (BDI), Lazarus and Folkman's coping inventory, and the Family Adaptability and Cohesion Scale (FACES III). Lymphocyte subtypes were quantified using flow cytometry.*

Results: *Links between immunity and depression were confirmed: levels of CD3, CD4 and CD8 cells accounted for 12.7% of the variance in the BDI ($p<0.001$, linear regression; LR). The depression–immunity pairing interacted with family dynamics, coping mechanisms, and gender. Dynamics in the family of origin explained 11.4%of the BDI score (LR) and 1% of CD3 and CD4 levels ($p<0.001$, Pearson's r). Coping mechanisms were associated with 12% of the BDI score ($p<0.001$, LR), and the capacity of distancing oneself from one's problems was associated with 10.3% of CD3, CD8, and CD16/56 levels ($p<0.01$, LR). BDI scores in women were 2.9 points higher than in men ($p<0.01$, $t=2.379$) and associated with a greater risk of immune depression ($p<0.001$, odds ratio=0.5).*

Conclusions: *External determinants (family), coping mechanisms, and internal determinants (such as gender) simultaneously influence a depression–immunity pairing. Sometimes these factors act more on the mood component, sometimes more on the immune component. The two components also interact closely with each other.*

Key words: *immunity – psychosomatic - depression*

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INTRODUCTION

Since the work of Selye (1956), we have known that stressful stimuli activate the hypothalamic–pituitary–adrenal axis through the release of catecholamines, which modify humoral and cellular immunity. This psycho-immunological theory makes it possible to forge links between immunity and depression. Two main lines of research have developed as a result. The first, and the oldest, takes stress as a starting point from which to explain immune depression. Reynaert et al. (1995, 2010) found lower levels of natural killer (NK) cell activity in patients with major depressive disorder as a function of their health locus of control, which was reversed with antidepressants.

The second line of research, which has received more attention in the past 10 years, takes as its starting point immune cell activation and the release of inflammatory cytokines (Blume et al. 2011) or C-reactive protein (Zorrilla et al. 2001) as the cause of depression. Wium-Andersen et al. (2013) showed that higher C-reactive protein levels are associated with a higher risk of developing an anxiety or mood disorder. These inflammatory responses have a neurotoxic effect, leading to neuronal micro damage, such as reductions in dendritic length, spines and branching, in the hippocampus and prefrontal cortex. In parallel, the production of brain-derived neurotrophic factor is inhibited (Wager-Smith et al. 2011), which delays neuronal regeneration. Furthermore, work by Maes et al. (2011) showed an increase in the CD25 lymphocyte count in depressed people, which were related to the percentage of CD4 lymphocytesand the CD4:CD8 ratio.

Our earlier research has found that, in depressed patients, correlations exist between:

- levels of CD3, CD4, CD16/56, and the family dynamic (Zdanowicz et al. 2015);
- levels of CD3, CD8, CD16/56, and the distancing coping strategy (Manceaux & Zdanowicz 2016);
- levels of CD3, CD8, lymphocyte percentage, and gender (Fagniart et al. 2016).

Although the links between immunity and family dynamics have never been investigated directly, ourearlier results reflect those reported by Gusta et al. (1994), who compared the effects of cohabitation and living alone on CD4 levels in monkeys, or those of Kiecolt-Glaser et al. (1993), who investigated immunological variations in conflicts between couples in humans.

To the best of our knowledge, there have been no studies that have investigated immunity in parallel with coping mechanisms. However, many studies of patients with cancer have indicated that stress, depression, coping with the disease, or a "type C" personality are contributing factors in the onset and/or course of the disease (Reynaert 2000). Here, we bring together these findings in a theory that describes a psychosomatic depression–immunity unit that operates as a pair.

SUBJECTS AND METHODS

We conducted an open-label trial over four years. All 549 patients hospitalized for a major depressive

episode in the Psychosomatic Department of the Cliniques Universitaires de Mont-Godinne, Belgium, were included. All subjects were Caucasian.

All patients admitted to the department completed a socio-demographic questionnaire (gender, ethnicity, employment status, marital status) and:

- A visual analogue scale of the severity of life events in the past month.
- The Beck Depression Inventory (BDI), consisting of 21 items.
- Olson's Family Adaptability and Cohesion Evaluation Scale (FACES III).
- Cousson's coping test: a 27-item checklist in French, based on the original version created by Lazarus and Folkman.

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 (Beck et al. 1988).

FACES III (Olson 1986) consists of 20 questions that provide a quantitative estimate of the cohesion and adaptability of a system – whether the nuclear family, the family of origin, or the current or ideal family or couple.

Coping is defined as a process of "constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (Lazarus et al. 1984). Lazarus and Folkman suggested two dimensions: problem-focused and emotion focused. Problem-focused coping, used when we feel we have control over the situation and thus can manage the source of the problem. Emotion-focused coping, used when we feel we cannot manage the source of the problem. A third dimension was added in 1996 (Cousson et al. 1996): social support seeking. In total, the coping scale comprised eight categories: confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape-avoidance, planful problem-solving, and positive reappraisal.

We performed routine flow cytometry analysis in all patients to measure the various lymphocyte populations identified by the antigenic properties of membrane markers, including:

- CD3: present on all T cells: helper/suppressor and cytotoxic (two subpopulations).
- CD4: 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.
- CD8: a marker of cytotoxic-T cells. Once activated, these cells are capable of targeted cell destruction. An increase in CD8 is associated with 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 types of neutropenia.
- CD4: CD8 ratio: a measure of the health of the immune system, for example in the progression of AIDS.
- CD16 and 56: are surface markers of NK cells. NK cells are capable of destroying their target in the absence of major histocompatibility complex. NK cells are non-T cells (i.e. CD3). NK cell lymphocytosis is common and usually reflects a mild and transient condition.
- CD19: a B cell surface protein. These cells produce immunoglobulin.

All statistical tests were performed using SPSS 22.0 parametric methods. Type 1 and 2 errors were taken into account, and no post-hoc tests were performed. Correlations were evaluated using Pearson's r, and the chi-square test was used to compare qualitative variables. Means were compared using Student's t-test. Linear or logistic regression was used for quantitative / qualitative 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

Relationship between depression and immunity

This association is already well known. In the literature, this statistical link is often represented as follows: the more severe the depression, the more immunity is reduced. In our study, the coefficient of variation was strongest in CD4 ($p<0.000$; $r=-0.175$), followed by CD3 ($p=0.015$, $r=-0.112$), CD16/56 ($p=0.014$; $r=-0.113$), and lastly in the CD4: CD8 ratio ($p=0.045$; $r=-0.093$). A linear regression model with these variables explained up to 12.7% ($p<0.000$) of the severity of depression.

It should also be noted that we corrected the intensity of depression for age, employment status, living with a partner, and life events in the previous month. The variables influencing depression were age (the older the subject, the less severe the depression; $p<0.000$, $r=-0.172$); living with a partner (patients who lived with a partner were more depressed than those living alone; $\Delta 3$ $p=0.007$, $t=2.7$) and life events ($p<0.000$, $r=0.248$). The same variables also influenced immunity: age was correlated with levels of CD3 ($p<0.000$, $r=0.151$), CD8 ($p<0.000$, $r=-0.252$), CD4 ($p<0.000$, $r=-0.167$) and CD16/56 ($p<0.000$, $r=-0.168$). Immune variables explained 15.4% of the variance of age (linear regression, $p<0.000$). Life events negatively

influenced the level of CD8 (p=0.014, r=−0.109). Living with a partner was associated with a lower level of CD3 (Δ 2.35 p<0.000, t=3.75), CD4 (Δ1.59 p=0.023, t=2.275), and CD16/56 (Δ 1.65 p<0.000, t=3.812). These immune variables represent a probability of 0.6 (logistic regression, odds ratio p<0.000) of living as a couple.

Link between family dynamics, depression and immunity

The relationship between depression and an individual's support group is well established. We previously explored links between family – specifically family dynamics – and depression severity (Zdanowicz et al. 2010, 2011a, 2011b, 2012). In the present study, it was the dynamic of the family of origin (the family in which the patient was raised) that was correlated with the severity of depression. The lower the cohesion and adaptability of the family of origin, the greater the present-day depression (cohesion, p=0.007, r=−0.169; adaptability, p=0.035, r=−0.133). A linear regression taking into account cohesion and adaptability explained 11.4% of the variance of depression severity (p<0.000). Although it is not unreasonable to suggest that depression leads to disruption in the relationships in the family of origin, the chronological order rather implies that a more cohesive and adaptable dynamic in the family in which we grow up offers a degree of protection against later depression.

In establishing whether there was a link between immunity and the family dynamic, we were surprised to discover that there is indeed a correlation, admittedly small, between both cohesion in the family of origin, with 1.1% of variance in the level of NK cells (p=0.019), and adaptability, with 0.08% of variance in the levels of CD3 (p=0.04) and CD4 (p=0.044).

It is difficult to imagine that a reduction in our immunity influences relations in our family of origin, and indeed the chronological order once again suggests that family relationships during our childhood seem to influence our immune response in later life. More comprehensively, it could even be said that the family relationships experienced during childhood offer a small degree of protection against a reduction in immunity concomitant with depression in later life.

Link between coping mechanisms, depression, and immunity

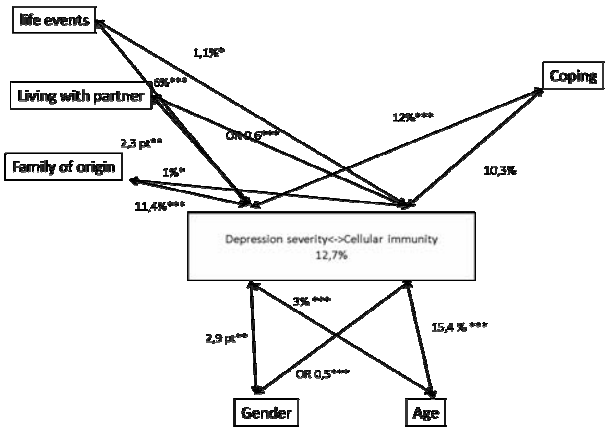
Our previous studies addressed relationships between coping mechanisms and severity of depression, and whether those mechanisms aggravated the depression or protected against it (Zdanowicz et al. 2016, 2015, 2014). In the present study, strategies such as planful problem solving or positive reappraisal seemed to protect against depression, as there was a negative correlation with the BDI score (planful problem solving, p<0.000, r=−0.216; positive reappraisal, p<0.000, r=−0.265). In contrast, escape–avoidance was associated with a greater severity of depression (p<0.000, r=0.218). Together, coping mechanisms explained 12% of the variance of the intensity of depression (linear regression, p<0.000). It was very surprising to note that although distancing oneself from one's problems was not significantly correlated with depression severity, this strategy was correlated with levels of CD3 (p=0.008, r=−0.114), CD4 (p=0.027, r=−0.095), CD8 (p=0.005, r=−0.119), CD19 (p=0.017, r=−0.102), and CD16/56 (p=0.029, r=−0.227). Together, these immune variables explained 10.3% of the variance of the level of distancing (linear regression).

Depression, immunity and gender

Gender has long been known to influence both the prevalence of depression and the prevalence of autoimmune diseases. In contrast, the influence of gender in the immune response in depressed patients has been the subject of far fewer investigations (Fagniart et al. 2016, Pitychoutis & Papadopoulou-Daifoti 2010). In the present study, it seemed that not only was the severity of depression more intense in women than in men (Δ 2.9, p=0.018, t=2.379) but above all, immune depression was greater in women than in men for CD3 (Δ −0.18 p=0.014, t=2.676), CD4 (Δ −0.14 p=0.012, t=2.522) and CD8 (Δ −0.05 p=0.003, t=2.182).

DISCUSSION

Taking into consideration the different components we have studied, our results indicate that the depression–immunity pairing lies at the intersection of internal and external determinants. It is influenced by external determinants such as living with a partner, life events, and family dynamics, which in turn are modulated by coping mechanisms. On the other hand, gender and age are internal determinants. At the centre of these interactions is the depression–immunity pairing, which, although not unequivocal, represents nearly 12.7% of the severity of depression (Figure 1).

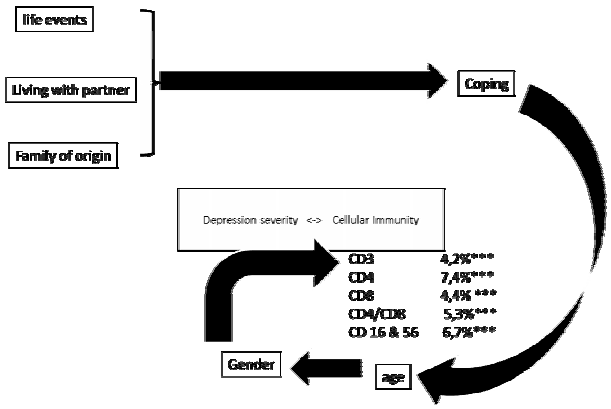


p<0.05, ** p<0.01, *** p<0.001

Figure 1. Depression–immunity association

Although it may be futile to attempt to identify whether depression causes immune suppression or whether it is an immune disease, there appears to be a psychosomatic unity in which interactions, depending on the circumstances, operate in one direction or the other. This leads us toconsider that treating depression using medication that acts on the immune system is a reasonable psychotherapeutic intervention for the treatment of an immune disorder. However, from this perspective, not all of the points of interaction we have identified have the same potential for bringing about change. It is clear, for example, that we cannot change the gender or age of the patient. Similarly, it would be very ambitious to consider modifying the family dynamic in which our patient grew up, although it must be highlighted that this factor carries more weight than recent life events. Acting on coping mechanisms, however, appears to be a good approach for simultaneously influencing depression and immunity, but it calls upon different strategies: planful problem solving and positive reappraisal for the affective component, and distancing for the immune component.

What is clearly missing in this theory of psychosomatic unity is a way to attribute a score to an individual's level of functioning, i.e. how to calculate a global depression–immunity score, especially given that all the lymphocyte populations (with the exception of CD19) are affected differently depending on the interacting variable. A linear regression, taking into account all the variables identified as having an influence on the lymphocytic populations, indicates that CD4 and CD16/56 are the most sensitive (Figure 2).



* p< 0.05, ** p < 0.01, *** p < 0.001

Figure 2. Percentage variance of lymphocytes

CONCLUSION

Together, our results suggest that external events (family dynamics, life events, living with a partner), how these external events are managed (coping mechanisms), and intrinsic determinants such as gender, influence the depression–immunity pairing. Sometimes these factors act more on the thymic component, sometimes more on the immune component. The two components themselves also directly influence each other. It is clear that the psycho-immunologic theory must be revisited from the perspective of a homeostatic relationship between depression and immunity; this concept may open the way for new therapeutic strategies.

Acknowledgements:

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors."

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008..

Conflict of interest: *None to declare.*

Contribution of individual authors:

All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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