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DEPRESSION, FAMILY AND IMMUNITY: INFLUENCE OF HUMORAL IMMUNITY ON FAMILY RELATIONSHIPS AND ON THE SEVERITY OF DEPRESSION

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SUMMARY

Background: *Previous study shows that cellular immunity and family relationships are each correlated with the severity of depression and suggests that the psycho-immunological theory should look at the relation between immunity and family life. The aim of the present study based on the same sample is to investigate if similar correlations exist with humoral immunity.*

Subjects and method: *498 inpatients with major depressive disorder were enrolled in an open-label trial. In addition to a socio-demographic questionnaire, they completed Olsen's FACES III and the Beck Depression Inventory (BDI). We performed a classic blood test, a plasma cortisol assay at 8 a.m., 4 p.m. and 8 p.m. and a dexamethasone suppression test (Carroll test). Electrophoresis is used for separation and quantification of serum proteins.*

Results: *There is no correlation between humoral immunity and the severity of depression. We found a correlation between cohesion of the family of the origin and beta-globulins (r=-0.147; p=0.016), and C4 (r=0.124; p=0.039). Between adaptability of the family of the origin and cortisol levels at 8 a.m. (r=0.122; p=0.008). We showed a correlation between both C4 (r=-0.263; p=0.000) and beta-globulins (r=-0.148; p=0.013) with CD8. There is a correlation between cortisol at 8 a.m. and CD4 (r=-0.095; p=0.033).*

Conclusions: *Humoral immunity has no correlation with depression but has multiple interactions with cellular immunity which is correlate with the severity of the depression. The psycho-immunological theory is reinforced. It is quite original to find correlation between the family functioning and C4 or beta-globulins while the link with cortisol strengthens some studies about psychological stress, cortisol and immunity. Future studies should examine which kind of family or relation are implicated and how the family functioning and immunity could be connected.*

Key words: *immunity – family – Olson – depression*

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INTRODUCTION

Relationships between immunity and depression have been demonstrated in several studies concerning both humoral and cellular immunity. Monocytosis, increased blood levels of interleukin (IL-1, IL-6) and tumor necrosis factor (TNF) are observed in acute episodes of major depression (Steiner 2011). Studies underlined the immune cell activation (Maes 2011) and the release of inflammatory cytokines (Blume 2011) or C-reactive protein (CRP) (Zorrilla 2001, Wium-Andersen 2013) as the cause of depression. It suggests a neurotoxic effect of inflammatory response particularly in the hippocampus and prefrontal cortex and the inhibition of BDNF production (Wager-Smith 2011). According to these studies, the psycho-immunological model would be a bidirectional model with both an effect of depression on the immune system and a role of immunity on depression.

We know that stressful events activate hypothalamo-pituitary-adrenal axis (HPA axis) releasing cortisol which alters the humoral and cellular immunity (Selye 1956). A biphasic model is proposed in which acute stress enhances and chronic stress suppresses the immune response (Dhabhar & McEwen 1997). There is evidences for overactivity of HPA axis and elevated circulating cortisol in major depressive disorder (Barden 2004). Vreeburg et al. (2009) found that both remitted and current major depressive disorder are correlate with higher cortisol awakening response. Lamers et al. (2013) showed that atypical depression is correlate with inflammatory and metabolic dysregulation while melancholic depression is rather correlates with hyperactivity of the HPA axis. Studies evoked that cortisol induces hippocampal and frontal-limbic circuits damages (Stokes 1995, Travis 2016, Liu 2016).

Stelzhammer et al. (2014) performed a molecular profiling study on serum samples from first onset antidepressant drug-naïve major depressive disorder patients. He shows that several circulating molecules are increased or decreased in people with depression compared to healthy controls. Particularly, there is evidences of pro-inflammatory proteins changes (IL-1, IL-16, macrophage migration inhibitory factor) and in particular an increase regarding some acute phase proteins such as ferritin or complement component C4b. Older studies showed this evidence concerning acute phase protein and a raise of C4 in depressed patients (Berk 1997, Song 1994). Moreover, Stelzhammer et al. showed a reproducible correlation between C4b and the severity of depression.

Zdanowicz et al. (2015) showed that cellular immunity and family relationships are each correlated with the severity of depression (respectively 12.7% and

11.4% of the variance) and have a greater effect in combination (16% of the variance) than individually. This cumulative effect underlines the interaction between family dynamics and cellular immunity. It suggests that the psycho-immunological theory should look at the relation between immunity and family life, notably in relation to the cohesion or adaptability of the family of origin. The aim of this study, based on the same sample, is to investigate if similar correlation exists with humoral immunity.

SUBJECTS AND METHODS

Our study is an open-label trial carried out over 4 years and includes all 498 patients hospitalized for a major depressive episode 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, the Beck Depression Inventory (BDI), the Olson's Family Adaptability and Cohesion Evaluation Scale (FACES III). All statistical tests were performed using SPSS 22 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. Selected significance levels were $p>0.95$ and $p<0.05$.

The BDI consists of 21 items and 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 2002).

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

A classic blood test is performed and also a plasma cortisol assay at 8 a.m., 4 p.m. and 8 p.m. A dexamethasone suppression test is realized as it was standardized by Carroll (1981). It consists to evaluate plasma cortisol concentration within 24 hours after administration of 1mg dexamethasone.

Cortisol is a steroid hormone (glucocorticoid) produced by the adrenal gland as a result of the activation of hypothalamic–pituitary–adrenal axis in response to stress. Cortisol have multiple functions in the body like blood sugar regulation and immune system suppression. Diurnal cycles of cortisol levels are found. The level peaks in the early morning (approximately 8 a.m.) and reaches its lowest level at about midnight - 4 a.m. Changed patterns of serum cortisol levels have been observed in clinical depression, psychological stress or physiological stressors like fever, illness, surgery or pain (Selye 1956, Barden 2004).

Immunoturbidimetry is used to measure the level of immunoglobulins and proteins of the complement system in the serum. The complement system can be activated by two independent pathways, the classical and the alternate complement pathways. The activation of classic pathway require antigen - antibody complex and factor C4 is a component of this pathway. This activation lead to anaphylactic/inflammatory activity or opsonization. C4 is a protein of the acute phase of inflammation, its concentration increases during inflammation. Its concentration is increased in systemic infectious diseases, and during non-infectious chronic inflammatory conditions (mainly chronic forms of rheumatoid arthritis). A decrease in C4 levels is the result of a peripheral consumption resulting of complement activation (immune complex disease, systemic lupus erythematosus, autoimmune thyroiditis and juvenile dermatomyositis)

Electrophoresis is used for separation and quantification of serum proteins. It's possible to separate albumin and globulins (alpha-1, alpha-2, beta and gamma globulins). The profil of migration is modified during some pathologies and notably during inflammatory or autoimmune diseases. We especially considered areas where proteins having a role in immunity as the immunoglobulin (gamma-globulins) or complement proteins (beta-2 globulins) are supposed to migrate.

RESULTS

Influence of socio-demographic variables on the severity of depression

The sample of depressed patients (N=498) is aged between 18 and 90 years with a mean of 48 years (SD=10). All subjects are Caucasian. Statistical analyses show that age ($p=0.000$; $r=-0.172$), life events in the past year ($p<0.000$; $r=0.248$), gender and domestic situation are significantly correlated with the severity of depression (Table 1). All the results are therefore control for these variables.

No correlation between humoral immunity and severity of depression

Table 2 shows that all cell classes are correlated with the severity of depression, with the exception of CD19. Note that CD4 and CD8 are both correlated with severity of depression.

Correlation between family relationships and humoral immunity

We don't show link between immunoglobulins level and family relationships. Table 3 shows Correlations between FACESIII and C4 or Beta-globulins and with cortisol level at 8 a.m. and after dexamethasone suppression test (carroll test). A correlation between CD4 and FACESIII was found. Particularly concerning cohesion ($r=-0.001$; $p=0.978$) and adaptability ($p=0.093$; $r=0.044$) within the family of the origin. No relation was observed between CD8 and FACESIII.

Table 1. Correlation between socio-demographic variables and the severity of depression

	N	BDI	t	p
Gender	Men (N=188)	27	2.492	0.013
	Women (N=310)	30		
Domestic situation	Relationship (N=242)	30	2.700	0.007
	Single (N=256)	27		
Employment status	Employed (N=243)	30	NS	
	Unemployed (N=255)	28		

BDI - means of BDI scores and were compared using Student's t-test; N - number of subjects; $p<0.05$ is statistically significant; NS - non significant

Table 2. Correlation between lymphocyte subsets and severity of depression

		Beck
CD3	r	-0.112
	p	0.015
CD4	r	-0.175
	p	0.000
CD8	r	0.080
	p	0.060
Ratio CD4/CD8	r	-0.093
	p	0.045
CD19	r	0.044
	p	0.346
CD16/56	r	0.113
	p	0.014

Table 3. Correlations between FACESIII and C4 or Beta-globulins and with cortisol levels at 8a.m. and after dexamethasone suppression test (Carroll test)

		Beta-globulins	C4	Cortisol (8:00 a.m.)	Cortisol (4:00 p.m.)	Carroll test (8:00 a.m.)
CD3	r	-0.147	0.124	0.085	0.055	-0.277
	p	0.016	0.039	0.063	0.238	0.018
CD4	r	-0.057	0.057	0.122	0.094	0.051
	p	0.350	0.341	0.008	0.042	0.670

Table 4. Correlations between lymphocyte subsets and some humoral immunity mediators (Beta-globulins, C4, immunoglobulins), with cortisol level at 8 a.m. and after dexamethasone suppression test (Carroll test)

		Beta-globulins	C4	IgM	IgG	Cortisol (8 a.m.)	Carroll test (8 a.m.)
CD3	r	-0.035	-0.207	0.178	0.193	-0.016	0.012
	p	0.552	0.000	0.001	0.000	0.725	0.921
CD4	r	0.088	0.089	0.018	-0.106	-0.095	0.136
	p	0.141	0.131	0.743	0.051	0.033	0.242
CD8	r	-0.148	-0.263	0.142	0.237	0.071	-0.148
	p	0.013	0.000	0.009	0.000	0.111	0.201
CD4/CD8	r	0.155	0.192	-0.111	-0.212	-0.047	0.103
	p	0.009	0.001	0.042	0.000	0.292	0.375
CD19	r	0.007	0.157	-0.127	-0.057	-0.107	-0.052
	p	0.903	0.007	0.020	0.292	0.016	0.656

Correlation between cellular and humoral immunity

Table 4 shows the existence of correlations between lymphocytes subsets and some humoral immunity mediators such as C4, Beta-globulins and immunoglobulins and correlations with diurnal cortisol levels. No corrélation was found between Carroll test and lymphocytes subsets.

Correlation between family dynamics and severity of depression

It is showed a correlation between family of origin cohesion and severity of depression ($r=-0.169$; $p=0.007$). There is also a correlation between family of origin adaptability ($r=-0.133$; $p=0.035$) and severity of depression.

DISCUSSION

Unlike cellular immunity no relationship could be demonstrated between humoral immunity and the severity of depression. As expected (Carnaud 1994, Male 2006) a relationship was observed between humoral immunity and lymphocyte subsets for which a link with the severity of depression was demonstrated in the previous study. So it is evoke an indirect relationship between the humoral immunity and the severity of depression. Moreover, it was possible to show a link between humoral immunity and family relationships. Correlations have been found firstly between certain circulating proteins involved in immunity mediated by antibodies (C4 and Beta-globulins) and the cohesion within the family of origin and secondly between cortisol level at 8 a.m. and the adaptability within the family of origin.

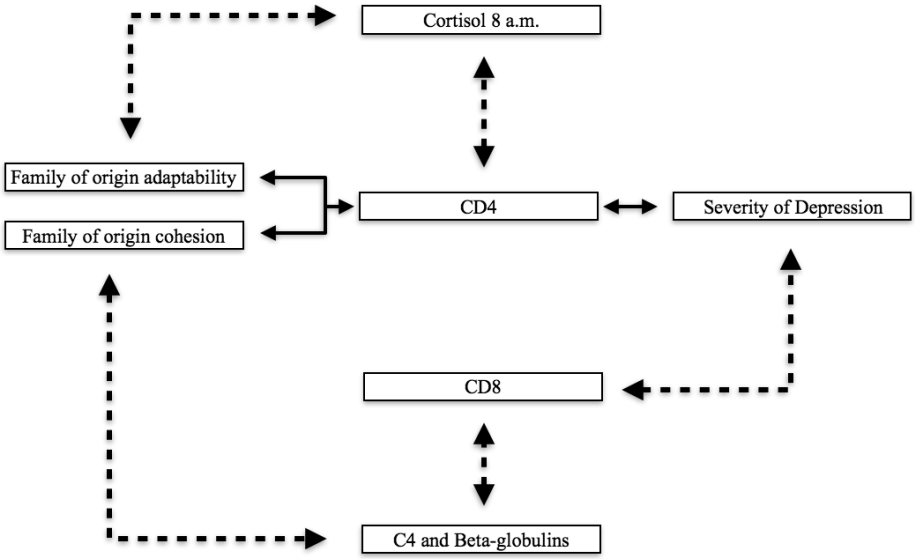

Figure 1. Links between family relationships, lymphocyte subsets (CD4 and CD8), humoral immunity and severity of depression

We highlighted the central role of lymphocytes CD4. It is both correlated with the severity of depression and cohesion as well as adaptability in the family of origin. On the other hand the CD8 although having a correlation with the severity of depression have no relation with family dynamics. In this study, we show that CD8 is correlated with C4 and beta-globulins which have a link with the cohesion of the family of origin. The hypothesis there is a link between immunity, depression and family relationships is strengthened by the fact that some factors of cellular immunity having no correlation with family relationships could be connected to it through a correlation with humoral immunity (Figure 1). It is showed that adaptability within the family of origin is not correlated with C4 or beta-globulin. Interestingly it appears to be related to the diurnal cortisol variations and more particularly with the morning cortisol (8 a.m.) which is also correlated with cellular immunity via CD4 (Figure 1).

Relations between depression and immunity are not new and this study reinforces the existence of a psycho-immunological model. According to this study, cellular immunity is at the forefront of this model and humoral immunity have only an indirect link with depression. The relationship between the severity of depression and family relationships is interesting but less surprising because it has already been showed in some studies (Pardoen 1996, Zdanowicz 2011). The most surprising fact is to find a link between family dynamics and both cellular and humoral immunity. Indeed find a relationship between cohesion within the family of origin and the C4 protein playing a role in the humoral immune response and which changes occur in inflammatory or systemic diseases is quite original. The relation between adaptability within the family of origin and cortisol is also interesting and strengthens some studies about psychological stress, cortisol and immunity (Segerstrom 2004). The link between stressful family events or early-life stress and the immune system is particularly well documented for cortisol levels (Steeger 2016, Jaffee 2015). Other factors as CRP or cytokines also appear to be involved (Lu 2013, Miller 2012). Furthermore this study show that the family functioning and the kind of relationship between family members have a link with the immunty. Future studies should examine which kind of family or relation are implicated and how the family functioning and immunity could be connected.

CONCLUSIONS

Humoral immunity has no correlation with depression but has multiple interactions with cellular immunity which is correlate with the severity of the depression. The psycho-immunological theory is reinforced. The hypothesis there is a link between immunity, depression and family is strengthened by the fact that some factors of cellular immunity having no correlation with family relationships could be connected to it through a correlation with humoral immunity.It is quite original to find correlation between the family functioning and C4 or Beta-globulins while the link with cortisol strengthens some studies about psychological stress, cortisol and immunity. Future studies should examine which kind of family or relation are implicated and how the family functioning and immunity could be connected.

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Conflict of interest: None to declare.

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