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Study on the Role of Inflammatory Markers and Type D Personality on Symptom Profiles and Severity in Patients with Major Depressive Disorder

Ileana Enatescu ¹, Raluka Kalinovic ², Catalina Giurgi-Oncu ^{2,3} , Vladimir Poroch ^{4,*} , Ioan Sorin Stratulat ⁴, Gabriela Vlad ², Oana Neda-Stepan ², Mihaela Simu ^{3,5}, Ion Papava ^{2,3} , Roxana Oancea ⁶, Raul Patrascu ⁷ and Virgil Radu Enatescu ^{2,3}

- ¹ Department of Obstetrics and Gynecology-Discipline of Childcare and Neonatology, “Victor Babes” University of Medicine and Pharmacy Timisoara, 2 Eftimie Murgu Square, 300041 Timisoara, Romania; enatescu.ileana@umft.ro
- ² “Pius Brinzeu” Emergency County Hospital-Psychiatric Clinic, 156 Liviu Rebreanu Blvd., 300723 Timisoara, Romania; raluka.kalinovic@hosptm.ro (R.K.); catalina.giurgi@umft.ro (C.G.-O.); gabriela.vlad@hosptm.ro (G.V.); oana.neda-stepan@hosptm.ro (O.N.-S.); papava.ion@umft.ro (I.P.); enatescu.virgil@umft.ro (V.R.E.)
- ³ Department of Neuroscience, “Victor Babes” University of Medicine and Pharmacy Timisoara, 2 Eftimie Murgu Square, 300041 Timisoara, Romania; simu.mihaela@umft.ro
- ⁴ 2nd Department of Internal Medicine, Grigore T. Popa University of Medicine and Pharmacy, 16 Universitatii Str., 700115 Iasi, Romania; ioan.stratulat@umfiasi.ro
- ⁵ “Pius Brinzeu” Emergency County Hospital-Clinic of Neurology II (M.S.), 156 Liviu Rebreanu Blvd., 300723 Timisoara, Romania
- ⁶ Discipline of Preventive Dentistry, Community and Oral Health, “Victor Babes” University of Medicine and Pharmacy Timisoara, 2 Eftimie Murgu Square, 300041 Timisoara, Romania; roancea@umft.ro
- ⁷ Department of Functional Sciences—Physiology, “Victor Babes” University of Medicine and Pharmacy Timisoara, 2 Eftimie Murgu Square, 300041 Timisoara, Romania; patrascu.raul@umft.ro
- * Correspondence: vladimir.poroch@umfiasi.ro

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Abstract: The high rates of chronicity and recurrences account for the limited efficacy of current antidepressants, conceived based on the current neurobiological hypotheses, in reaching the full clinical and functional remission of major depressed (MDD) patients. We aimed to analyze the role of pro-inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6), respectively, and type D personality (TDP) on the depressive symptoms measured by the 17-item Hamilton Depression Rating Scale (HAM-D). The processed data are part of a prospective 8-weeks follow-up study conducted in 50 subjects with MDD referred to ‘Eduard Pamfil’ Psychiatric Clinic Timisoara. The presence of elevated pro-inflammatory markers in MDD patients with TDP has been significantly associated with higher somatic anxiety ($p = 0.005$) and somatic symptoms-general ($p = 0.016$) mean rank scores compared to their counterparts without significant inflammation. The combination of increased CRP and IL-6 levels were significantly correlated with higher impaired insight ($p = 0.026$) mean rank scores, additionally. The presence of a significant level of IL-6 has shown a significant effect of size ($p = 0.023$) on the severity of major depression at baseline. On the contrary, type D personality has not influenced the severity of depressive symptoms ($p > 0.05$). Inflammatory markers significantly impact the clinical profiles and symptoms severity of MDD patients.

Keywords: depression; inflammatory markers; chronic medical comorbidity; psychopathology

1. Introduction

Major depressive disorder (MDD) is among the most prevalent psychiatric disorders in the general population, having a high rate of psychiatric comorbidities [1,2]. In our country, studies have found notable frequencies of depressive symptoms in distinct clinical subpopulations [3,4].

Albeit the most treatable psychiatric condition, only about one-third of MDD patients achieve remission in the first treatment step of antidepressant therapy [5]. There is a growing body of evidence suggesting that many other underlying biological mechanisms should be considered to develop new classes of antidepressant drugs [6].

Research data has evidenced that the neurotransmitters' imbalances result in an overactivated response of immune systems through the HPA (hypothalamic-pituitary-adrenal) and sympathoadrenal medullary (SAM) axes dysfunction [7]. On the one hand, increased level of norepinephrine (NE) results in activating of macrophages by increased DNA binding of nuclear factor (NF)- κ B in peripheral blood mononuclear cells, finally leading to the release of inflammatory mediators that promote inflammation (e.g., acute phase reactants, adhesion molecules, chemokines, and pro-inflammatory cytokines such as tumor alpha necrosis factor, IL-1 β , and IL-6). On the other hand, the increased secretion of corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus, through the adrenocorticotrophic hormone ACTH released by the pituitary gland, stimulates the cortisol production. Furthermore, persistent hypercortisolemia leads to the desensitization of glucocorticoid receptors existing on the surface of the lymphocytes resulting in a decreased capacity to suppress the hyperimmune response by the cortisol and dexamethasone [6,7].

Recently, the gut microbiome has become a subject of interest for the research of human diseases, considering that about 70% of the body's immune cells reside in the gut-associated lymphatic tissue (GALT). Thus, the neuroinflammatory response to stress can be determined by two pathways leading to increased susceptibility to depressive-like behaviors. Firstly, the peripheral Th17 cells (possibly released from the lamina propria of the small intestine) may infiltrate the brain parenchyma. Secondly, surveying cluster of differentiation 4 CD4 + T cells may differentiate into Th17 cells in situ after receiving signals from proinflammatory cytokines (e.g., IL-6, IL-1b, tumor necrosis factor TNF) generated during the neuroinflammation [8].

The relationship between brain, neurotransmitter systems, and altered immune response to stress has been emphasized by other studies [9,10]. For instance, patients with higher levels of C-reactive protein (CRP), a non-specific acute-phase protein increased during systemic inflammation, were at risk of developing depressive symptoms [11–13]. Moreover, it has been found that a higher level of CRP, in women but not in men, was associated with increased severity of depressive symptoms on Montgomery Aasberg Depression Rating Scale (MADRS). One explanation of the authors was that it might be a differential modulation of immune responses by sex hormones in women compared to men [14].

Conversely, non-steroidal anti-inflammatory drugs (NSAIDs) have been proven to have neuroprotective and antidepressant effects in animal and human studies [15]. However, NSAIDs should be administered only in MDD patients with elevated levels of pro-inflammatory markers as one study has revealed that NSAIDs attenuated antidepressant effects of SSRIs in both animal and human models for depression as well as in STAR*D trial participants [16].

Finally, the presence of pro-inflammatory markers was associated with the resistance to antidepressant treatment [17]. Other studies have evidenced that CRP might be a biological marker of treatment response to antidepressant treatment [18,19].

The current study aimed to investigate the hypothesis that pro-inflammatory markers (CRP and IL-6) and type D personality could shape the symptomatic profile and alter the severity of depressive symptoms in MDD patients.

2. Materials and Methods

The processed data are part of a larger prospective 8-week follow-up study [20]. Hence, 52 initial patients with MDD who addressed or were referred to the 'Eduard Pamfil' Psychiatry Clinic Timisoara for psychiatric assistance, were invited to take part in the present study. Of these, two patients subsequently declined to attend all assessment during distinct moments of study.

The inclusion criteria were to fulfill Diagnostic and Statistical Manual of Mental Disorders IV "text revision" TR (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for Major Depressive Disorder, single or multiple episode, based on Romanian version of Structured Clinical Interview for DSM-IV-TR Axis I Disorders Manual-IV-TR SCID-I [21], aged 18 or above, providing written informed consent.

The exclusion criteria were presence of DSM-IV-TR Axis I major psychiatric disorder other than Major Depressive Disorder, presence of pregnancy, the participant is unable to provide informed consent, presence of acute inflammatory disease.

The sampling method was by convenience. The recruitment period was between April 2016 and September 2019.

At baseline, all patients were assessed for depressive symptoms by administering the 17-item Hamilton Depression Rating Scale (HAM-D) by trained psychiatrists. Also, CRP and IL-6 were measured in blood serum.

All sociodemographic, case history and clinical data were collected in the same standardized and unitary manner.

The study was approved by the Local Ethics Committee for Scientific Research registration number: 7/01.02.2016 of the Timisoara County Emergency Hospital where the patients were recruited, all subjects providing written informed consent, also respecting the Helsinki Declaration of 1975 regarding research on human subjects.

The severity of depressive symptoms was measured by using the 17-item Hamilton Depression Rating Scale (HAM-D). The HAM-D, a clinician-administered depression assessment scale, consists of 17 items pertaining to symptoms of depression experienced over the past week. A score ranging from 0 to 7 is generally accepted to be within the normal or in clinical remission, while a score of 20 or higher is considered indicating at least moderate severity. In our study, the resulted scores were only treated from a quantitative perspective without using a cut-off score [22].

Type D personality (TDP) was surveyed by applying the Type D Scale-14 DS 14 that comprises of 14 items, which is a Likert scale where each item can be scored between 0 = false to 4 = true. Furthermore, the DS-14 scale consists of two subscales representing two distinct dimensions of TDP already described in the introduction section; one is Negative Affectivity evaluated by seven items, and the other is Social Inhibition, which is measured by the other seven items. The total score on each subscale is between 0 and 28. The use of the DS 14 scale is dichotomic, requiring a score ≥ 10 on both subscales to fulfill the D personality condition [23]. Furthermore, based on an extensive cross-cultural equivalence analysis that included 22 European countries and English-speaking countries, the DS14 had good reliability with Cronbach's α between 0.80 and 0.90 for NA and between 0.74 and 0.89 for SI in all countries, except for Russia [24].

For measurement of C-reactive protein (CRP) and interleukin 6 (IL-6), fasting blood was drawn by venipuncture in clot activator vacutainer tubes for serum separation. Blood processing and CRP and IL-6 determination in serum was performed in a certified clinical laboratory (Bioclinica Laboratories, Timisoara, Romania). CRP was determined by a latex-enhanced immunoturbidimetric method using the Atellica CH Wide Range C-Reactive Protein assay (Siemens Healthineers, Munich, Germany) according to the manufacturer's recommendations in an Atellica CH Analyzer (Siemens Healthineers). Serum IL-6 levels were determined using a sandwich ELISA method with the Cobas Elecsys IL-6 assay (Roche Diagnostics, Rotkreuz, Switzerland) according to the manufacturer's instructions.

All statistical analyses were done within STATA version 15 and a p -value < 0.05 was statistically significant. The Chi-square test was used to compare the frequencies of analyzed data. Non-parametric tests, such as the Mann–Whitney U and Kruskal–Wallis tests, were used to compare the mean ranks of ordinal data. Spearman’s rank correlation coefficient was calculated to evaluate the intensity and direction of relationship between ordinal variables. The comparisons have considered either two strata (with and without significant levels of inflammatory markers) or three strata (the significant presence of inflammatory markers was further divided into two subcategories—only significant CRP levels and both CRP and IL-6 significant levels). The comparison of HAM-D items mean ranks were done only in MDD patients with type D personality to increase the homogeneity of the compared strata knowing that the TDP may have a significant influence on the analyzed scores. An ANOVA factorial test was done to estimate the effect of size of the presence of inflammatory markers and type D personality and their interactions on HAM-D depression scores at the baseline of the study. The type D personality was used as the nominal dichotomic variable. The presence of inflammation (CRP and/or IL-6) was treated both as a nominal dichotomic and quantitative variable depending on the statistical analyses.

3. Results

3.1. Demographic Data and Type D Personality Stratified by the Presence Inflammatory Markers

Of total patients, 31 (62.0%) had not significant levels of pro-inflammatory markers, 12 (24.0%) had significant CRP levels, and 7 (14.0%) had significant levels of both CRP and IL-6, respectively. The distribution of type D personality depending upon the pro-inflammatory strata has not differed significantly ($p = 0.779$) as follows: non-inflammatory strata 45.2%, significant CRP increased level alone 33.3% and both CRP and IL-6 elevated levels 42.9%, respectively (Table 1).

Table 1. Demographic characteristics of the studied group depending on the peripheral elevated pro-inflammatory markers

Baseline Demographic Data and Type D Personality	Without Significant Pro-Inflammatory Markers, n = 31	With Significant CRP Levels, n = 12	With Significant CRP and IL-6 Levels, n = 7	p-Value
Average current age (SD) ^a	49.84 (11.708)	45.83 (11.519)	53.00 (13.166)	0.419
Gender-male, n (%) ^b	7 (22.6%)	3 (25.0%)	1 (14.3%)	0.856
Educational level, mean ranks ^c	25.73	22.83	29.07	0.616
Residency-Urban area, n (%) ^b	21 (67.7%)	5 (41.7%)	7 (100.0%)	* 0.033
Professional status-Employed or Student, n (%) ^b	12 (38.7%)	8 (66.7%)	3 (42.9%)	0.252
Marital status-with intimate partner, n (%) ^b	22 (71.0%)	6 (50.0%)	5 (71.4%)	0.406
TDP, n (%) ^b	14 (45.2%)	4 (33.3%)	3 (42.9%)	0.779

Note: *—The level of significance for all analyses was set at $\alpha = 0.05$; ^a—One-Way ANOVA test; ^b—Chi-Squared test; ^c—Kruskal Wallis test; TDP—type D personality; CRP—C-reactive protein; IL6—Interleukin-6; The listed percentages are reported to either strata considered separately.

Regarding the baseline demographic data, the only significant difference was related to residency, subjects with both elevated pro-inflammatory markers were living more frequent in urban areas ($p = 0.033$) compared to the others (Table 1).

3.2. Depressive Symptoms Profiles Depending upon the Presence of Peripheral Pro-Inflammatory Markers in Major Depressed Patients with Type D Personality.

Considering the influence of peripheral pro-inflammatory markers in MDD patients with type D personality, the presence of elevated peripheral pro-inflammatory has been significantly associated with higher somatic anxiety ($p = 0.005$) and somatic symptoms-general ($p = 0.016$) mean rank scores.

Although they did not reach the threshold of statistical significance, it should be noted that most items of the HAM-D scale showed higher mean scores in MDD patients with personality D and proinflammatory markers present compared to their non-inflammatory counterparts. Exceptions were items related to early and middle sleep disorders and weight loss (Table 2).

Table 2. Depressive symptoms profile depending on the presence or absence of peripheral inflammatory markers (in comparison with subjects with normal blood levels) in MDD patients with type D personality

HAM-D Items	MDD Subjects with TDP and Non-Significant Inflammatory Markers ^a (n = 14)	MDD Subjects with TDP and Elevated Inflammatory Markers ^a (CRP and/or IL6) (n = 7)	p-Value
1. Depressed Mood	10.61	11.79	0.649
2. Feelings of guilt	10.68	11.64	0.714
3. Suicide	10.50	12.00	0.568
4. Insomnia—early	12.14	8.71	0.162
5. Insomnia—middle	11.57	9.86	0.517
6. Insomnia—late	10.57	11.86	0.624
7. Work and Activities	10.57	11.86	0.628
8. Retardation	9.50	14.00	0.102
9. Agitation	10.18	12.64	0.349
10. Anxiety—psychic	9.82	13.36	0.183
11. Anxiety—somatic	8.46	16.07	* 0.005
12. Somatic symptoms—GI	10.29	12.43	0.403
13. Somatic symptoms—General	8.99	15.21	* 0.016
14. Genital symptoms	10.46	12.07	0.532
15. Hypochondrias	10.29	12.43	0.405
16. Weight loss	11.96	9.07	0.264
17. Insight	11.00	11.00	1.000

Note: HAM-D—the 17-item Hamilton Depression Rating Scale; GI—gastrointestinal; ^a—the listed figures represent mean ranks; Mann–Whitney U Test was used to compare the mean ranks of patients without significant inflammatory markers and the two subgroups of elevated inflammatory markers (only CRP and both CRP and IL-6, respectively).
*—The level of significance for all analyses was set at $\alpha = 0.05$.

3.3. Effect Size of Peripheral Pro-Inflammatory Markers and Type D Personality on the Baseline HAM-D Scores of Studied Subjects

The significant level of peripheral IL-6 has shown a significant effect of size ($p = 0.023$) on the severity of major depression at baseline. Conversely, type D personality has not influenced the severity of depressive symptoms ($p > 0.05$) (Table 3).

Table 3. Effect size of peripheral pro-inflammatory markers and type D personality on the baseline depressive symptoms.

Significantly Associated Risk Factors	F	p-Value	Df	Partial Eta Squared
IL-6	5.577	* 0.023	1	0.115
CRP	0.687	0.412	1	0.016
Type D personality	0.276	0.602	1	0.006
IL-6*CRP	0.180	0.673	1	0.004
IL-6*Type D personality	0.642	0.427	1	0.015
CRP*Type D personality	0.300	0.300	1	0.025
IL-6*CRP*Type D personality ^a	-	-	0	<0.001

*—The level of significance for all analyses was set at $\alpha = 0.05$; CRP, C-reactive protein; IL6, Interleukin-6; ^a—few numbers of cases; Factorial ANOVA test-R Squared = 0.463 (Adjusted R Squared = 0.358).

4. Discussion

The presence of pro-inflammatory markers was overly represented in studied subjects compared to other researches [25,26]. The size of the studied group alongside the sampling method may also have contributed to this result.

Except residency, baseline demographic data were mostly comparable considering the stratified subgroups based on peripheral pro-inflammatory markers, the presence of IL-6 being the strongest associated pro-inflammatory marker with urbanicity. It seems that, at least in part, the pollution may play a role to the more present inflammatory markers in those living in urban areas compared to rural areas [27,28].

Over recent decades, the mind–brain relationship has elicited the interest of many neuroscientists. Within the conscious psyche, all new information is processed based on pre-existing cognitive schemas developed and structured, especially in early childhood. Persistent and pervasive dysfunctional schemas lead to a biased and negatively processing of the new information that functioning as general rules based on which the objective reality is subjectively interpreted and organized in the conscious psyche [29]. By extension of this widely accepted psychological paradigm, as dysfunctional cognitive schemas underlie the negative affective experiences through the erroneous interpretation of objective reality, it seems that type D personality individuals are subject to the same biased interpretation of their health status, eventually leading to a more amplified negative affectivity and autonomic overactivity [30].

Several neuroendocrine and neurobiological substrates are thought to be involved in the mind–heart interactions. Consequently, the HPA (hypothalamic–pituitary–adrenal) and sympathoadrenal medullary (SAM) axes dysfunction (that are brought together under the name of the neuro–cardiac axis), chronic low-grade inflammation, endothelial cells dysfunction, neurotransmitters imbalances, altered level of neurotrophic factors, and the dysconnectivity of cortico-subcortical neural networks are presumed to uphold the effect of psychological stress on MDD patients with type D personality [6]. These pathophysiological processes may also account for the higher comorbidity between distinct physical illnesses—namely dyslipidemia, hypertension, diabetes mellitus, and obesity—which are also highly correlated with both MDD and stress-related conditions, including type D personality. Moreover, it would comprehensively connect the higher scores of anxiety items of HAM-D with the peripheral pro-inflammatory markers found in our research.

There could be a superposition between the subjective psychological symptoms expressed by anxiety symptoms associated with MDD and the physical symptoms of medical conditions in which inflammation could play a critical role. In this case, we are discussing a state of comorbidity between two distinct diseases that must be investigated carefully, and both conditions should adequately be treated to obtain remission. In this respect, other research data have already evidenced that MDD is a highly comorbid major psychiatric disorder [31–33]. Furthermore, MDD with highly significant somatic complaints could represent a specific subtype of depressive experiences in patients with elevated levels of inflammatory responses. In the latter situation, the symptoms expressed at the bodily level have a functional character and the antidepressant treatment will also cause the improvement of these symptoms. Somatic-like symptoms represent only a distinct facet of the clinical expression of MDD that, to some extent, may be considered a result of a chronic inflammatory state. Due to the overexpression of somatic manifestations in the subgroup of MDD patients and both CRP and IL-6 elevated levels, the origin of the symptoms may be inappropriately assigned to other diseases, the most probable to a physical condition rather than to MDD [34,35].

Lastly, the presence of pro-inflammatory cytokines would probably shape the clinical expression and the severity of MDD. Furthermore, extensive studies should be conducted to identify this hypothetical distinct phenotype of MDD with elevated underlying inflammatory markers.

5. Conclusions

Finding innovative pathogenic mechanisms underlying MDD could open up new avenues for novel classes of psychotropic medication or the development of more clinical efficient therapeutic algorithms. Thus, the involvement of inflammatory markers in MDD is a clinical state of fact.

We consider that the detection of inflammatory markers should become a routine and feasible clinical approach, and add-on celecoxib treatment would be warranted in MDD cases with coexisting chronic inflammatory processes.

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