Journal of Affective Disorders 249 (2019) 410–417

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Reduced CXCL1/GRO chemokine plasma levels are a possible biomarker of elderly depression

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ARTICLE INFO

Keywords:
Major depression
Inflammation
Cytokines
Chemokines
Biomarkers
Cytokine weighted score

ABSTRACT

Background: Depression is the single largest contributor to non-fatal health loss worldwide. A role of inflammation in major depressive disorder (MDD) was suggested, and we sought to determine if cytokine levels predict the severity of depressive symptomatology or distinguish MDD patients from healthy controls (HCs).
Methods: The severity of depressive symptoms and cognitive impairment were assessed by the Korean version of the Geriatric Depression Scale (GDS-K) and Mini-Mental State Examination (MMSE-KC) in 152 elderly subjects (76 with MDD). Plasma levels of 28 cytokines were measured and analysed as continuous predictors or dichotomized using the median value. The association between individual cytokines, MDD risk and depressive symptoms severity was investigated using multiple logistic and linear regressions that included the relevant covariates. A Cytokine Weighted Score (CWS) was calculated by weighting cytokines according to previously reported effect sizes on MDD risk. Sensitivity analyses were performed excluding subjects with significant cognitive impairment.
Results: CXCL10/IP-10 levels were higher in subjects with MDD vs. HCs while the opposite was observed for CXCL1/GRO. Only the second association survived after adjusting for possible confounders and excluding subjects with severe cognitive impairment. Using dichotomized cytokine levels, CXCL1/GRO and TNF-α were negatively associated with MDD. The CWS was also negatively associated with MDD. Cytokine levels did not predict the severity of depressive symptoms.
Limitations: Our cross-sectional approach was not able to longitudinally evaluate any temporal fluctuations in the considered cytokine levels.
Conclusions: This study found significantly lower CXCL1/GRO chemokine plasma levels in elderly subjects with MDD compared to HCs.

1. Introduction

Depression is the single largest contributor to non-fatal health loss worldwide, and it accounts for 7.5% of global Years Lived with Disability (YLD) (WHO, 2017). In the elderly, depression is linked to poorer performance in all cognitive domains, and it is associated with an increased risk of dementia and all-cause mortality (Butters et al., 2004; Diniz et al., 2013, 2014).

A number of studies have confirmed a role of inflammation and immunity in the pathogenesis of major depressive disorder (MDD) (Rosenblat et al., 2014). For instance, the release of inflammatory mediators, following an external pathogenic insult, is able to elicit depression-like symptomatology, better known as sickness behavior. This syndrome is characterized by the coexistence of anhedonia, drowsiness,

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https://doi.org/10.1016/j.jad.2019.02.042
Received 8 November 2018; Received in revised form 11 February 2019; Accepted 12 February 2019
Available online 13 February 2019
0165-0327/

behavioral inhibition, anxiety and cognitive symptoms (Maes et al., 2012). In line with this finding, the use of pegylated interferon (INF)-α in HCV (Hepatitis C Virus) infection therapy has been associated with the onset of moderate/severe depressive symptoms in more than 20% of treated patients (Machado et al., 2017; Pavlovic et al., 2011).

Several mechanisms are probably implicated in the pathogenesis of the sickness behavior. It has been demonstrated that pro-inflammatory cytokines are able to activate the enzyme indoleamine-2,3-dioxygenase (IDO) (O'Connor et al., 2009a), which subtracts tryptophan from the pathway of serotonin synthesis. The IDO-mediated metabolism of tryptophan along the kynurenine pathway is responsible for the production of 3-hydroxy-kynurenine (3OH-KYN) and quinolinic acid (QUIN) (Dantzer et al., 2011). These metabolites may be responsible, among the other effects, for a decreased astrocytic reuptake of glutamate and an overproduction of reactive oxygen species (ROS), both events associated with increased neurotoxicity (Santamaria et al., 2001; Tavares et al., 2002). QUIN may also produce overstimulation of the N-methyl-D-aspartate (NMDA) receptor, therefore inducing apoptosis and hippocampal atrophy (Wichers and Maes, 2004). In addition, increased production of inflammatory cytokines may also be responsible for the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and peripheral resistance to glucocorticoids (Zunszain et al., 2011), which in turn amplifies the inflammatory response.

Inflammation has also been implicated in antidepressant response. Indeed, molecular pathways involved in inflammation were associated with antidepressant response (Fabbri and Serretti, 2015) and treatment-resistant depression (TRD) cases benefits from augmentation strategies with substances having effects on inflammation pathways such as lithium, selective cyclooxygenase-2 inhibitors (COXIB) or omega-3 polyunsaturated fatty acids (PUFAs) (Akhondzadeh et al., 2009; Nelson et al., 2014; Schefft et al., 2017).

Several meta-analyses have summarized the evidence reported in individual studies about altered cytokines levels in MDD patients compared to healthy controls (HCs) (Eyre et al., 2016; Goldsmith et al., 2016; Haapakoski et al., 2015; Valkanova and Ebmeier, 2013). One of the most recent meta-analyses found that blood levels of CCL2/MCP-1, IL-1ra, IL-6, IL-10, IL-12, IL-13, IL-18, sIL-2r, sTNFr2 and TNF-α were elevated in patients with MDD compared to HCs, whereas IFN-γ levels were lower in MDD (Köhler et al., 2018). Considering only physically healthy individuals, higher peripheral levels of CCL2/MCP-1, CCL3/MIP-1α, CCL11/Eotaxin, CXCL7/PPBP, CXCL8/IL-8 and decreased CCL4/MIP-1β were reported in patients with MDD compared to HCs (Leighton et al., 2018).

On the contrary, some studies did not detect any increase in pro-inflammatory cytokines in MDD (Cassano et al., 2017; Cilan et al., 2013; Marques-Deak et al., 2007). It is worth considering that inflammation may contribute to depression only in a subset of patients since MDD is a heterogeneous disorder (Kiecolt-Glaser et al., 2015). Contrasting results may also derive from the coexistence of many confounding factors, including stress and comorbidity with physical diseases.

Taking into account the effect of potential confounding variables, this study aimed to determine if individual peripheral cytokine levels were associated with: 1) the severity of depressive symptoms in patients with MDD, and 2) the risk of MDD. Furthermore, we hypothesized that a weighted score including multiple cytokines previously associated with MDD might be associated with MDD risk.

2. Material and methods

2.1. Study population

The participants were recruited from the Ansan Geriatric (AGE) cohort study. The AGE study was a prospective population-based cohort study aiming to collect comprehensive information on the overall health and functional status of the elderly population, conducted in Ansan-si (province of Gyeonggi-do), South Korea. The detailed study protocol and research design of the AGE study have been previously described (Han et al., 2009). In the first wave of the study, 1391 participants were randomly selected from September 2004 to March 2006. The data used in this study were part of this cohort. Of the 1391 participants, 777 were assessed for MDD using the Korean version of the Mini-International Neuropsychiatric Interview (MINI) (Yoo et al., 2006). A final research diagnosis of MDD was derived, based on a consensus meeting of a psychiatrist, a clinical psychologist and a neurologist. The disease onset was dated after the age of 60 for all the patients with MDD.

As a result, the number of non-depressed and depressed subjects in the cohort was 653 and 124, respectively. Among them, 76 HCs and 76 subjects with MDD were selected by random sampling to be included in this study. Indeed this sample size was expected to provide enough power to detect effect sizes similar to those reported by previous studies (Cohen's $d = 0.46$ at $p = 0.05$, e.g. (Leighton et al., 2018)). All MDD except six patients were antidepressant-free at study inclusion, because subjects were collected based on a community-based cohort study, not in a clinical trial setting (Han et al., 2009).

Socio-demographic and health-related data were collected at baseline, including history of medical diseases, use of antidepressant and anti-inflammatory drugs. Depressive symptoms were assessed in accordance with the Korean version of the 30-item Geriatric Depression Scale (GDS-K). The GDS is a self-reported scale used for the assessment of depression in the elderly population that shows high sensitivity and specificity (McGivney et al., 1994; Smarr and Keefer, 2011).

To evaluate the overall cognitive function, the Korean version of the Mini-Mental State Examination (MMSE-KC) was used (Lee et al., 2002a).

All participants provided written informed consent. The study protocol was approved by the institutional review board of the Catholic University of Korea Bucheon St. Mary's Hospital and Korea University Ansan Hospital (HC14EISI0040).

2.2. Plasma cytokine levels measurement

Plasma samples were analysed by multiplexing with Milliplex® Map Human Cytokine/Chemokine Magnetic Bead Panel (Millipore®, Billerica, MA, USA) using a Luminex xMAP® platform (Luminex® Corporation, Austin, TX, USA) to detect and evaluate the results, according to the manufacturer's protocol (accessible at http://www.merckmillipore.com). Further information about the measurement procedure is available in Supplementary Methods (paragraph 1). The full list and abbreviations of the peripheral measured cytokines are reported in Table S1. All cytokine levels (in pg/mL) were $\log_{10}$ transformed to reduce the skewness of data and normalize their distributions.

2.3. Statistical analysis

As primary outcome, continuous cytokine levels were tested for possible differences between MDD cases and controls and as predictors of depressive symptom severity in MDD.

As secondary outcome, the same analyses were repeated using dichotomized plasma cytokine levels through a median split procedure to divide the distribution of data into two equal groups, avoid skewness problems and the creation of very small subgroups that would reduce power. Despite dichotomized outcomes provide lower power than continuous variables, it is possible that biological effects do not follow a linear variation and differences may be seen only for those having the highest values.

Only cytokines having non-detected (missing) values $< 20\%$ were included in the analyses, similarly to what done in previous studies (Bot et al., 2015; Decker et al., 2017). Cytokine values that were outside 3 SD (standard deviations) from the mean and $>$ 1 SD from the

distribution tails were considered outliers and removed from the analyses. This led to exclusion of only the 0.5% of the measured values.

Firstly, differences between patients with MDD and HCs were evaluated by the Chi-square test and Student's *t*-test or Mann–Whitney *U* test as appropriate. Then, logistic and linear regression analyses were applied to test the described hypotheses. Wald chi-square statistics was used to assess the significance of logistic regression models, being the case/control (MDD/healthy) status the binary dependent variable. For each tested linear regression model, normal probability plots and scatter diagrams of observed residuals versus predicted residuals were examined to avoid violations of normality and linearity. Age, gender, BMI, smoking attitude, alcohol consumption, use of NSAIDs (non-steroidal anti-inflammatory drugs) and antidepressants were included as covariates based on previous literature evidence (Crews et al., 2006; Darnall and Suarez, 2009; Köhler et al., 2018; O'Connor et al., 2009b; Schachter et al., 2018; Wiedlocha et al., 2018). Indeed, background information from previous literature and known biological connections between the outcome and/or the predictors with possible confounders are relevant for the choice of covariates in a relatively small sample such as the present one. Gastro-enteric comorbidities were also included among the covariates because of their association with the most part of the analysed cytokines in our sample. Use of antidepressants was included as covariate in the linear models but not in the logistic regression models because of a complete separation issue, which occurs when an outcome variable separates a predictor variable completely or almost completely. Indeed, in our sample, only six subjects were on antidepressant treatment and, among them, all were in the MDD group. We decided to not include among covariates demographic factors that differed between MDD cases and HCs when their role in the modulation of MDD risk could be attributed to indirect effects depending on complex interactions with other variables (e.g. education may have an effect depending on the interaction with a number of other variables such as socio-familiar background, risk of somatic disease, BMI and smoking patterns (e.g. (Gilman et al., 2008)).

Finally, we calculated a Cytokine Weighted Score (CWS) to account for the cumulative contribution of cytokines previously associated with MDD in the two most recent meta-analyses (Köhler et al., 2017; Leighton et al., 2018). Further details about the computation of the CWS are available in Supplementary Methods (paragraph 2).

For all the tested associations, we performed two sensitivity analyses: 1) subjects with severe cognitive impairment (MMSE-KC scores ≤ 18) were excluded; 2) MDD patients who were not during an acute disease phase or had sub-threshold MDD (GDS-K scores ≤ 10) were excluded. Indeed, these subjects could be a source of heterogeneity in the evaluation of cytokine levels. GDS may perform worse in subjects with severe cognitive impairment (Montorio and Izal, 1996) and cytokine alterations may vary depending on the phase of depressive illness (Eyre et al., 2014). For those cytokines showing differences between MDD and HCs, we also performed an exploratory analysis to evaluate if a similar difference could be detected also when comparing sub-threshold MDD cases ($n = 10$) and HCs.

All data were analysed using STATISTICA version 12 (StatSoft Inc., 2014 - www.statsoft.com). Nominal (unadjusted) p-values were reported. After Bonferroni correction for multiple comparisons was applied to the linear and logistic regressions, the significance threshold was adjusted to $\alpha = 0.002$ ($\alpha = 0.05/28$).

For the analysis of between groups differences in continuous cytokine levels, our sample provided enough power (0.80) to detect a Cohen's $d = 0.65$ at α level $= 0.002$.

3. Results

3.1. Socio-demographic and clinical characteristics of the sample

A total of 152 participants were included in the study, 76 in the control group and 76 in the depressed group. Patients with MDD were significantly older, less likely to be married or to live with a partner, they were more frequently women, they had lower education and lower alcohol consumption compared to controls. There were no differences for the other relevant clinical-demographic characteristics, except the use of antidepressants obviously. The detailed clinical and socio-demographic characteristics of the sample are summarized in Table 1.

3.2. Comparison between patients with MDD and healthy individuals

28 of the 41 (68.3%) measured cytokines met the criteria for inclusion in our analyses (further details are in Table S1). Several biomarkers showed higher mean values in MDD patients (CXCL10/IP-10, IL-1α and VEGF), but only CXCL10/IP-10 remained significant after multiple-testing correction ($p < 0.002$). Conversely, CCL2/MCP-1, CCL5/RANTES, CCL22/MDC, CXCL1/GRO, EGF, IL-5, IL-17A, PDGF-AB/BB and TNF-α showed lower mean values in MDD patients; only CXCL1/GRO remained significant after multiple-testing correction ($p < 0.002$). The results are summarized in Table S3. For CCL5/RANTES, CCL22/MDC, CXCL1/GRO, CXCL10/IP-10, EGF, IL-5, PDGF-AB/BB, TNF-α and VEGF the significance was exclusively driven by

Table 1
Sociodemographic and clinic characteristics of the study groups (total $n = 156$). Values are means (SD: standard deviation) unless otherwise mentioned.

Variable	Healthy controls ($n = 76$)	Patients with MDD ($n = 76$)	Test statistics	*p*-value
Age	66.17 (3.75)	68.05 (4.90)	$t = -2.66$	< 0.05
Women, n (%)	43 (56.58)	60 (78.9)	$\chi^2 = 8.70$	< 0.05
Married or living with a partner, n (%)	63 (82.89)	48 (63.2)	$\chi^2 = 7.51$	< 0.05
Smoking (current), n (%)	50 (65.79)	55 (72.4)	$\chi^2 = 0.77$	< 0.05
Education (≤ 6 years), n (%)	28 (31.0)	52 (70.8)	$\chi^2 = 15.20$	< 0.0-02
Education (7 to 12 years), n (%)	34 (37.9)	21 (25.0)	$\chi^2 = 4.81$	< 0.05
Education (≥ 13 years), n (%)	14 (31.0)	3 (4.2)	$\chi^2 = 8.01$	< 0.05
Alcohol use ≥ 3 times/week, n (%)	19 (25.0)	9 (11.8)	$\chi^2 = 4.38$	< 0.05
BMI, kg/m^2	24.95 (3.51)	25.05 (2.96)	$t = -0.2$	0.845
GDS-K scores	6.38 (7.46)	18.03 (5.72)	$t = -13.58$	< 0.0-02
MMSE-KC	26.95 (2.31)	23.89 (4.49)	$t = 5.27$	< 0.0-02
Use of NSAIDs, n (%)	9 (11.84)	14 (18.42)	$\chi^2 = 1.28$	0.258
Use of Antidepressants, n (%)	0 (0)	6 (7.89)	–	–
Gastro-enteric Diseases, n (%)	19 (25.0)	26 (34.21)	$\chi^2 = 1.15$	0.283

Abbreviations: t = Student's unpaired *t*-test; $\chi 2$ = Pearson Chi-square test; MDD, major depressive disorder; BMI, body mass index; GDS-K, Korean version of the Geriatric Depression Scale; MMSE-KC, Korean version of the Mini-Mental State Examination; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2
Association of the plasma cytokine levels (log_{10} transformed) with MDD diagnosis (case/control status), controlling for gender, age, BMI, smoking habit, alcohol consumption, use of NSAIDs, gastro-enteric comorbidities.

Cytokines	Wald stat.	*p*-value	OR	Lower CI	Upper CI
CCL11/Eotaxin	0.052	0.820	0.772	0.084	7.109
CCL2/MCP-1	7.984	< 0.05	0.032	0.003	0.347
CCL22/MDC	4.662	< 0.05	0.081	0.008	0.793
CCL4/MIP-1β	0.539	0.463	1.841	0.361	9.395
CCL5/RANTES	5.509	< 0.05	0.205	0.055	0.770
CCL7/MCP-3	0.027	0.869	1.134	0.255	5.046
CX3CL1/Fractalkine	4.106	< 0.05	4.389	1.050	18.353
CXCL1/GRO	13.052	< 0.002 **	0.045	0.008	0.243
CXCL10/IP-10	2.717	0.099	4.367	0.757	25.203
CXCL8/IL-8	2.414	0.120	0.509	0.218	1.193
EGF	3.190	0.074	0.461	0.197	1.078
FGF-2/bFGF	2.187	0.139	0.247	0.039	1.577
G-CSF	0.255	0.613	0.704	0.180	2.748
GM-CSF	0.415	0.519	0.632	0.156	2.553
IFN-α2	0.380	0.538	1.418	0.467	4.307
IFN-γ	1.383	0.240	0.541	0.194	1.506
IL-12p70	0.000	0.986	0.988	0.274	3.564
IL-17A	3.888	< 0.05	0.402	0.163	0.995
IL-1ra	1.225	0.268	0.508	0.153	1.687
IL-1α	1.958	0.162	1.940	0.767	4.906
IL-5	3.452	0.063	0.274	0.070	1.074
IL-7	0.298	0.585	0.715	0.214	2.386
PDGF-AA	4.054	< 0.05	0.227	0.054	0.961
PDGF-AB/BB	3.270	0.071	0.361	0.120	1.089
sCD40L	1.893	0.169	0.310	0.058	1.644
TGF-α	0.347	0.556	0.672	0.179	2.522
TNF-α	8.564	< 0.05	0.063	0.010	0.401
VEGF	6.716	< 0.05	4.398	1.435	13.480

Abbreviations: OR, odds ratio; CI, 95% confidence interval; BMI, body max index; MDD, major depressive disorder; NSAIDs, non-steroidal anti-inflammatory drugs.

** Significant results after Bonferroni correction ($\alpha = 0.002$ (0.05/28)).

differences between HCs and patients in acute phase of MDD, whereas the nominal significance for IL-17A was only caused by differences between HCs and non-acute patients, as revealed by an independent *t*-test. Nonetheless, the nominal significance for CCL2/MCP-1 and IL-1α was determined by both acute and non-acute patients (data are not shown). No significant differences were found for the other cytokine levels between HCs and patients with MDD.

Then, using multiple logistic regression analyses and accounting for the aforementioned confounders, we found that subjects with higher CXCL1/GRO levels had a lower risk of MDD after Bonferroni correction ($p < 0.002$). At a nominal significance level ($p < 0.05$), we found that subjects with higher CX3CL1/Fractalkine and VEGF had a higher probability to be diagnosed with MDD, whereas subjects with higher levels of CCL2/MCP-1, CCL5/RANTES, CCL22/MDC, IL-17A, PDGF-AA and TNF-α had a lower probability to be diagnosed with MDD. The results are summarized in Table 2.

After removing nine subjects with MMSE-KC scores ≤ 18 (severe cognitive impairment) from the analyses, IL-17A lost its nominal significance. Furthermore, we observed a slight decrease in the level of association for CX3CL1/Fractalkine and TNF-α as while a slight increase in significance for CCL2/MCP-1, CCL22/MDC and VEGF, although only CCL2/MCP-1 approached the Bonferroni-adjusted significance threshold. This sensitivity analysis had no consequence on the effect of CCL5/RANTES and CXCL1/GRO, which remained nominally and statistically significant, respectively. Detailed results are shown in Table S4. The removal of ten patients with GDS-K scores ≤ 10 (non-acute phase of MDD) from the analyses had no substantial effect on our results (data are not shown).

After the dichotomization of the cytokine plasma levels (secondary analyses), CXCL1/GRO and TNF-α levels were associated with reduced MDD risk after Bonferroni correction ($p < 0.002$). At a nominal significance level ($p < 0.05$), high CX3CL1/Fractalkine levels were associated with higher MDD risk, whereas the opposite was observed for FGF-2/bFGF and IL-17A levels. Detailed results are shown in Table S5.

A bar plot of the CXCL1/GRO, CXCL10/IP-10 and TNF-α distributions in HCs and patients with MDD is depicted in Fig. 1.

Finally, subjects with higher CWS had a lower probability of being in the MDD group ($p = 0.003$, OR = 0.10, 95% C.I. 0.02–0.47). The removal of nine subjects with MMSE-KC ≤ 18 had no substantial effect on this result ($p = 0.004$, OR = 0.11, 95% C.I. 0.02–0.49), see Table S6. The result remained significant after the removal of patients in the non-acute phase of MDD (data are not shown).

3.3. Association between cytokine plasma levels and depressive symptom severity in MDD patients

Taking into account the effect of possible confounders and after Bonferroni correction, the individual cytokine levels did not predict depressive symptom severity (GDS-K scores) in patients with MDD. At the nominal significance level, multiple regression analyses revealed that plasma levels of CCL5/RANTES, IL-1ra, IL-7, PDGF-AB/BB and sCD40L were negatively associated with GDS-K scores in patients with MDD (detailed results are shown in Table S7; scatterplots of nominally significant associations are available in Supplementary Figs. S1–S5).

After removing nine subjects with MMSE-KC ≤ 18 from the analyses, G-CSF gained a nominally significant negative association with depressive symptoms, whereas PDGF-AB/BB and sCD40L lost their nominal significance. With the same approach, we observed a decrease in significance for the negative association of CCL5/RANTES and a slight increase in significance for the negative association of IL-1ra and IL-7, despite none of these results was significant after multiple-testing correction. Detailed results are shown in Table S8. The removal of ten patients with GDS-K scores ≤ 10 (non-acute phase of MDD) from the analyses had no substantial effect on our results (data are not shown).

After the dichotomization of cytokine levels (secondary analyses), higher CCL4/MIP-1β and IL-7 levels had a nominal negative association with depression symptom severity (detailed results are shown in Table S9).

4. Discussion

The present study tested if peripheral cytokine levels show differences between MDD patients and HCs in a cohort of elderly subjects, and whether cytokine levels might predict the severity of depressive symptoms in MDD. Depression in the elderly may be influenced to a larger extent by inflammatory mechanisms, partly through the promotion of vascular pathophysiology (Taylor et al., 2013).

After correction for multiple comparisons and taking into account potential confounders, we found lower CXCL1/GRO levels in subjects with MDD vs. HCs, while the positive association between CXCL10/IP-10 level and MDD disappeared after adjusting for potential confounding factors. The effect of CXCL1/GRO on MDD risk was confirmed using dichotomized cytokine levels. These results were not affected by the exclusion of subjects with severe cognitive impairment. CXCL1/GRO belongs to the C-X-C chemokine family, and it is a chemotactic cytokine able to stimulate angiogenesis (Strieter et al., 1995) and the recruitment of neutrophils (Geiser et al., 1993). CXCL1/GRO signaling is triggered by a G-protein coupled receptor, the C-X-C receptor 2 (CXCR2), which has been identified in microglia, neurons and oligodendrocyte progenitors (OPGs) (Horuk et al., 1997; Lee et al., 2002b; Nguyen and Stangel, 2001). CXCR2 signaling is able to revert the CXCL10-CXCR3 induced apoptosis by limiting the activation of the caspase-3 protein. In addition to its neuroprotective effects, CXCR2 signaling plays a key role in the development of functional synapses, and it may be important in synaptic plasticity (Semple et al., 2010). Despite the role of CXCL1/GRO in neuroplasticity is still far from being fully elucidated, our

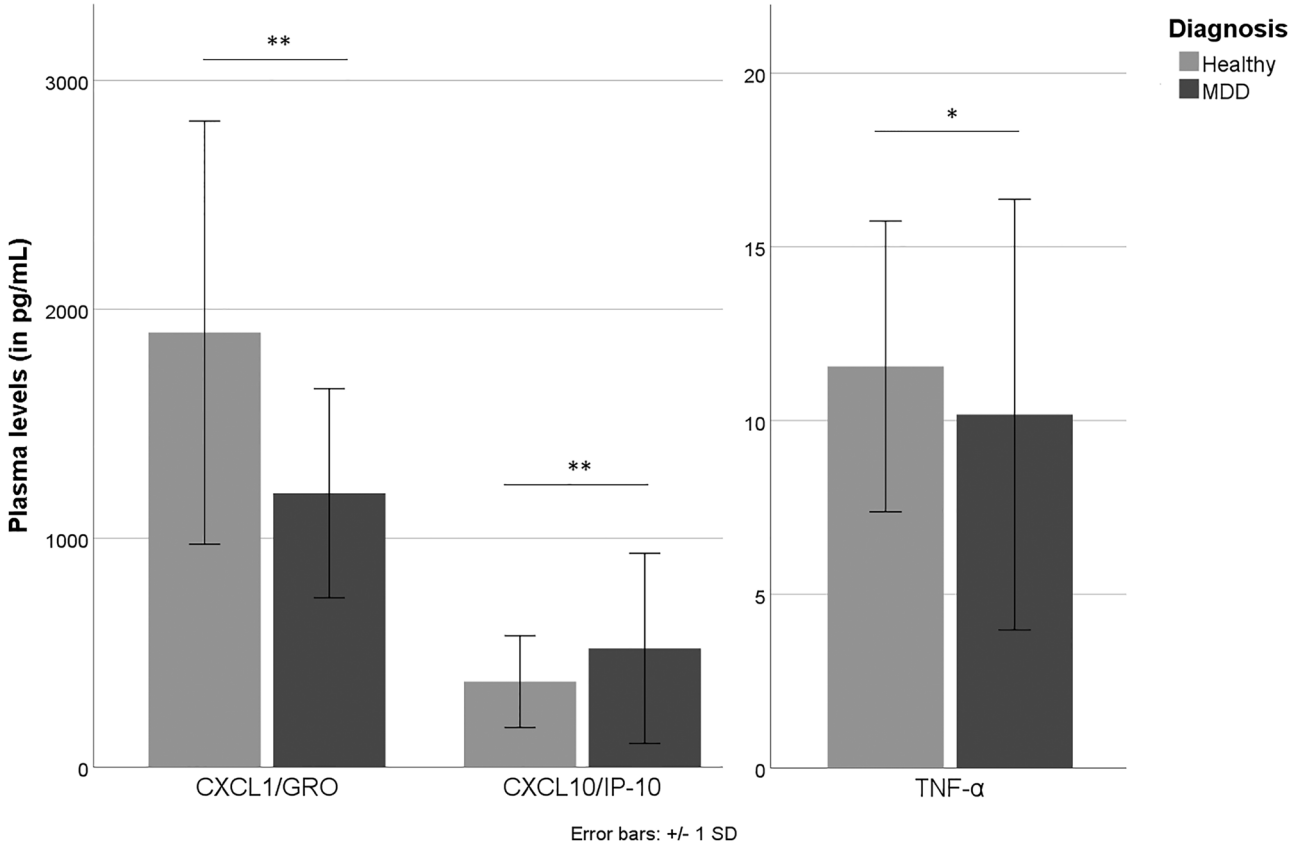

Fig. 1. Distribution of the mean values (± SD: standard deviation) of CXCL1/GRO, CXCL10/IP-10 and TNF-α plasma levels (in pg/mL) in healthy individuals and patients with MDD. Abbreviations: MDD, major depressive disorder. Significance level at *t*-test: ** $p < 0.002$, * $p < 0.05$.

findings suggest that this chemokine may be decreased in MDD cases compared to HCs, and the mechanisms mediating this association might involve putative CXCL1/GRO effects on neuroprotection and neuroplasticity, processes that are known to be altered in MDD (Castren, 2013; Marsden, 2013). However, our interpretation should be considered with much caution, since other chemokines also exert their action by binding to the same CXCL1/GRO receptor (Baggiolini et al., 1997). In line with our finding, lower serum CXCL1/GRO levels have been previously associated with MDD (Bot et al., 2015; Walss-Bass et al., 2018). A lower transcription of *CXCL1* was also reported in MDD, although this result was not subsequently confirmed in a validation step (Powell et al., 2014). By contrast, the expression of *CXCL1/GRO* was induced in the hippocampus and prefrontal cortex (PFC) in a mouse model of IFN-α-related depression (Hoyo-Becerra et al., 2015), suggesting that the increase of its expression may represent an early attempt to counteract the pathogenetic alternations associated with depression, but this mechanism may exhaust with the progression of the disease.

CXCL10/IP-10, another member of the C-X-C chemokine family, showed higher levels in MDD patients vs. HCs, but the effect was no longer observed after adjustment for potential confounders. CXCL10/IP-10 mediates the onset of sickness behavior and the cognitive dysfunctions induced by viral infections through an impairment of hippocampal synaptic plasticity (Blank et al., 2016). Some authors have previously reported an increase of CXCL10/IP-10 peripheral levels in MDD (Ho et al., 2017; Wong et al., 2008) and the effectiveness of antidepressants in reversing this abnormality (Wong et al., 2008).

The analyses using dichotomized cytokine levels showed a significant negative association between TNF-α and MDD. TNF-α is produced by astrocytes and microglia within the central nervous system (CNS). Several studies have shown increased TNF-α levels in depression and sickness behavior as well as decreased levels in treatment-responsive patients (Dantzer, 2001; Furtado and Katzman, 2015). Noteworthy, under physiological conditions, TNF-α in the CNS has also neuroprotective and neurotrophic effects through the modulation of neurotrophic factors and glutamate signaling (Figiel, 2008). It shows a pivotal role in synaptic scaling, which is a form of post-synaptic homeostatic plasticity (Beattie et al., 2002). Thus, the association between low levels of TNF-α and MDD in our sample might indicate altered synaptic homeostasis as well as an impaired neuroprotective and neurotrophic action.

Other associations with MDD risk were only nominally significant, including the positive association of CX3CL1/Fractalkine and VEGF and the negative association of CCL2/MCP-1, CCL5/RANTES, CCL22/MDC, FGF-2/bFGF and IL-17A. CCL2/MCP-1 approached the statistical significance threshold when subjects with severe cognitive impairment were removed from the analyses.

Contrary to what was expected, MDD diagnosis was associated with a lower Cytokine Weighted Score (CWS). The opposite direction of the effect in our sample compared to previous studies was mostly driven by trends of lower levels of CCL2/MCP-1 and TNF-α in MDD compared to HCs, although these individual effects were not significant. There are several hypotheses that could explain these contradictory results. First, not all MDD patients show increased levels of inflammatory cytokines (Brambilla and Maggioni, 1998; Marques-Deak et al., 2007; Steptoe et al., 2003) as well as only a minority of subjects with increased inflammation or treated with IFN-α develop MDD (Lotrich et al., 2007). Therefore, it is likely that higher levels of inflammation are noticeable only in a subset of patients with MDD, corresponding to a subtype of MDD. For example, compelling evidence links inflammation to the atypical depression subtype (Lamers et al., 2016). In this regard, the dissection of heterogeneous and complex pathologies in individual symptomatic domains, for example, according to the Research Domain Criteria (RDoc), could be a more effective strategy for studying

biomarkers in psychiatry (Treadway and Leonard, 2016). Furthermore, the distinction between pro- and anti-inflammatory cytokines represents a simplistic classification, since the same mediator of inflammation can determine an opposite effect depending on the nature of the target cell, the timing of exposure to that mediator and the nature of the triggering signal (Cavaillon, 2001), as we discussed for TNF-α. Cytokine levels were not able to predict the severity of depressive symptoms in patients with MDDin our sample. The only cytokine approaching statistical significance was G-CSF, which was negatively associated with GDS-K scores, after removing subjects with severe cognitive impairment. In addition to stimulating the bone marrow to produce granulocytes (UniProtKB), G-CSF may induce neurogenesis and neuroplasticity and prevent apoptosis in the CNS (Schneider et al., 2005). By contrast, higher IL-1ra and CCL4/MIP-1β levels were previously associated with increased symptom severity (Milaneschi et al., 2009; Oglodek and Just, 2018). Although some associations with depressive severity have been described for CCL2/MCP-1, CCL11/Eotaxin, CXCL/IL-8, TNF-α and VEGF, we have not detected any effect of these cytokines on the GDS-K scores in our sample (Huckans et al., 2014; Jung et al., 2015; Lavebratt et al., 2017; Oglodek et al., 2017; Suarez et al., 2004; Walsh et al., 2016).

Our results should be interpreted taking into account some limitations. First of all, our cross-sectional approach was not able to evaluate temporal fluctuations and intra-individual variation of the parameters taken into consideration. MDD is associated with a higher fluctuation of symptoms (Peeters et al., 2006) and this may correspond to a dynamic fluctuation of inflammatory biomarkers themselves and not all our MDD patients were during an acute phase of illness. On the other hand, this did not affect our findings as demonstrated by excluding patients with sub-thresholds GDS-K scores. Not all the factors that may affect cytokine levels were taken into account, such as early adversities or stressful life events (Kiecolt-Glaser et al., 2015) and duration of the depressive episode (Dunjic-Kostic et al., 2013). GDS may not maintain its validity in people with severe cognitive impairment, but this was addressed by doing a sensitivity analysis. In addition, GDS could reflect more a subjective than objective depressive symptomatology, because of its self-report nature (Montorio and Izal, 1996; Smarr and Keefer, 2011). We did not perform independent replication of our findings and our sample had an adequate power to detect an effect size (Cohen's $d = 0.65$ at the corrected alpha level $= 0.002$) that was slightly larger than the effect sizes reported by a previous meta-analysis (Cohen's d up to 0.48) (Leighton et al., 2018). Finally, it is worth noting that multiplexed Luminex-based measurement methods have some advantages (they are cost-effective and allow the simultaneous measurement of multiple proteins in limited sample volumes), but also some limitations. Indeed, such measurements may be affected by cross-reactivity between analytes and multiple antibodies in the assay (Chen and Schwarz, 2017; Leng et al., 2008). Most importantly, multiplex immunoassays may have difficulty in detecting low-abundance cytokines with sufficient sensitivity, specificity and reproducibility, particularly for some cytokines including those that we failed to detect in a sufficient number of samples (> 80%), such as IL-1β, IL-2, IL-4 and IL-6 (Belzeaux et al., 2017; Breen et al., 2011; Chaturvedi et al., 2011).

In conclusion, this study found significantly lower CXCL1/GRO levels in elderly subjects with MDD compared to HCs and this association may be mediated by the regulatory effect of this cytokine on excitotoxicity and neural plasticity. The effect of another chemokine of the C-X-C family came up (CXCL10/IP-10) which modulates synaptic plasticity, but its effect disappeared after considering confounding variables. The CWS was associated with the risk of MDD but in the opposite direction compared to what was expected, mainly as a result of trends of lower levels of CCL2/MCP-1 and TNF-α in MDD vs. HCs. As discussed, this should not be necessarily interpreted as a false positive finding, because the effect of chemokines/cytokines largely depends from the nature of the target cell, the timing of exposure and the nature of the triggering signal. Future studies should aim to evaluate in a longitudinal way the effect of relevant biomarkers and improve our knowledge on cytokine activity in the CNS, since they may show different effects depending on the cell type or specific region of the brain considered.

Declaration of interest

Prof. Alessandro Serretti is or has been consultant/speaker for Abbott, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier. The other authors declare no potential conflict of interest.

Role of funding source

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (grant number: HC15C1405).

Contributors

Giuseppe Fanelli performed the analyses, interpreted the results and wrote the first draft of the manuscript. Alessandro Serretti, Chi-Un Pae and Chiara Fabbri designed the study, helped with the interpretation of the results and reviewed the first draft of the manuscript. Chiara Fabbri supervised the whole process leading to the final paper. The other authors contributed to data collection, data preparation and/or the improvement of the final version of the paper. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.02.042.

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