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Published in:
The World Journal of Biological Psychiatry

DOI:
10.1080/15622975.2022.2095439

Publication date:
2022

The World Journal of Biological Psychiatry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iwbp20

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To cite this article: Irina A. Mednova, Lyudmila A. Levchuk, Anastasiia S. Boiko, Olga V. Roschina, German G. Simutkin, Nikolay A. Bokhan, Anton J. M. Loonen & Svetlana A. Ivanova (2023) Cytokine level in patients with mood disorder, alcohol use disorder and their comorbidity, The World Journal of Biological Psychiatry, 24:3, 243-253, DOI: 10.1080/15622975.2022.2095439

To link to this article: https://doi.org/10.1080/15622975.2022.2095439

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
2023, VOL. 24, NO. 3, 243–253
https://doi.org/10.1080/15622975.2022.2095439

ORIGINAL INVESTIGATION

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Cytokine level in patients with mood disorder, alcohol use disorder and their comorbidity

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ABSTRACT

Objectives: Because alcohol use disorder (AUD) is often accompanied by mood disorder (MD) and both alcoholism and depression result in activation of the immune system, this study compares serum cytokine levels in the presence of co-morbidity with those in either AUD or MD alone.

Methods: In this naturalistic prospective study the levels of 15 different cytokines were measured in serum samples of patients with MD ($n = 43$), participants with combined AUD-MD ($n = 44$) and AUD without MD ($n = 42$). The levels were compared cross-sectionally among themselves and with those in 50 healthy volunteers.

Results: Pro-inflammatory IFN-2α levels were consistently significantly higher and anti-inflammatory IL-1RA significantly lower in all study groups in comparison to healthy volunteers. In the MD only group we found increased IL-6 ($p = 0.001$), IL-7 ($p = 0.001$) and IL-13 ($p = 0.006$) levels, and decreased TNFα ($p = 0.0001$), IL-1RA ($p = 0.012$), IL-10 ($p = 0.002$) compared with group MD + AUD. Patients with AUD only showed elevated levels of IL-1β ($p = 0.046$), IL-2 ($p = 0.004$), IL-7 ($p = 0.0001$), IL-4 ($p = 0.049$) and IL-13 ($p = 0.015$) in contrast with MD + AUD group.

Conclusions: Because the interactions of alcohol with peripheral and cerebral immune systems are multifaceted, the pertinent connection to the mechanism how alcohol consumption contributes to the development of mood disorders cannot be properly explored.

ARTICLE HISTORY
Received 13 April 2022
Revised 16 June 2022
Accepted 24 June 2022

KEYWORDS
Alcohol use disorder; depressive mood disorder; cytokines; serum levels; habenula

Introduction

According to data from the Global Burden of Diseases studies, mental and addictive disorders affected more than 1 billion people globally in 2016. They caused 7% of all global burden of disease as measured in DALYs and 19% of all years lived with disability (Rehm and Shield 2019). Higher rates of depression were seen in women, while rates of substance use disorders, including alcohol use disorder (AUD) were higher in men (Rehm and Shield 2019). Given the high prevalence of depression and AUD in the general population, co-occurrence of these diseases is expected. A recent systematic review found a 2.4 increased lifetime risk of depression in alcohol use disorders (Saha et al. 2022). Conversely, a 2005 systematic review of 35 studies found a median current and lifetime prevalence of alcohol use disorders in depression of 16% (range 5%–67%) and 30% (range 10%–60%), respectively (Sullivan et al. 2005) and a recent meta-analysis of 39 studies found a prevalence of 0.208 (95% CI 0.183, 0.235) of individuals with major depressive disorder who also abused alcohol (Hunt et al. 2020). Comorbidity of affective and addictive disorders leads to worsening in clinical and dynamic indicators, levels of social adaptation and cognitive functions of patients, and also treatment dropout, suicide attempts, and poorer effect of antidepressant medication (Sullivan et al. 2005; Neupane 2016; Vasilieva et al. 2021). However, the mechanisms by which one disorder affects another remain unclear.

There are a number of common pathogenetic mechanisms of depression (Loonen and Ivanova 2016a) and alcoholism, in particular, impaired serotonin

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Supplemental data for this article can be accessed at https://doi.org/10.1080/15622975.2022.2095439.

metabolism, imbalance in hypothalamus–pituitary–gonadal and hypothalamus–pituitary–adrenocortical axis, and dysfunction of the immune system (Neupane 2016; Loonen and Ivanova 2016a; Walther et al. 2016; Underwood et al. 2018). We have previously found a decrease in Brain-Derived Neurotrophic Factor and Neural Cell Adhesion Molecules levels in AUD with and without concomitant mood disorder compared with healthy individuals (Levchuk et al. 2020). There is evidence that with excessive and/or prolonged activation of the cytokine network, a deterioration of neural plasticity can be observed (Miller et al. 2009) and therefore, in this study, we decided to focus on studying specific functions of the immune system.

After initial criticisms, an involvement of cytokines in the pathophysiology of depression has now become widespread acknowledged (Miller et al. 2009; Loonen and Ivanova 2016a), however the directionality of this relationship has not yet been elucidated. An increase in the level of a number of pro-inflammatory cytokines is observed against the background of a decrease in anti-inflammatory cytokines in the cerebrospinal fluid, serum and blood plasma of patients with depression (Dowlati et al. 2010). Decreased baseline levels of interleukin IL-6 and IL-8 were found in patients who later responded to antidepressant treatment (Lanquillon et al. 2000; Liu et al. 2020).

Acute and moderate alcohol use is thought to be associated with suppression of inflammatory responses, and chronic heavy alcohol use is thought to increase inflammation (Szabo and Mandrekar 2009). Increased C-reactive protein levels have been demonstrated in the presence of nicotine, alcohol, and cannabis use and nicotine dependence in adolescents and young adults (Costello et al. 2013). In patients with AUD IL-6 level was positively associated with depression and psychological distress scores, while IL-10 was negatively associated with anxiety score (Martinez et al. 2018).

From the above data, it can be inferred that the neuroimmune system plays at least some role in both the development of alcohol dependence and depressive mood disorder and that this results in changes in the levels of inflammation-related immune factors. Exactly what this connection looks like and what the interaction is with the comorbid mood disorders in alcohol use disorder has not yet been sufficiently explored. In an effort to gain some perspective on this, in the current study we compare cytokine levels in patients with AUD with and without mood disorder (MD), and in healthy individuals.

Materials and methods

Design

In a cross-sectional naturalistic study, the serum cytokine levels were compared across three diagnostic groups (patients with "pure" MD, patients with "pure" AUD, patients with comorbidity of AUD as well as MD (AUD-MD)), and healthy controls. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013), and approved by the Institutional Medical Review Board (Protocol of the local ethics committee at the Research Institute of Mental Health № 101 from 13 June 2017). All participants provided written informed consent.

Participants

Patients with MD ($n = 43$), participants with AUD-MD ($n = 44$) and AUD without MD ($n = 42$), were recruited from the departments of affective and addictive states of Mental Health Research Institute of the Tomsk National Research Medical Centre. Inclusion criteria were: a diagnosis of AUD (F10.2), MD (F31, F32, F33, F34.1) according to ICD-10 (World Health Organization 2004), or their comorbidity; ages 18–60 years. We excluded patients with other comorbid mental disorders, for instance schizophrenia, intellectual disability, and alcoholic psychoses, and patients with acute physical diseases. All participants had not taken any psychopharmacological drugs within 6 months prior to admission. The screening for relevant pathology for in/exclusion of subjects, disease development and the severity of the condition was performed through clinical assessment by three trained psychiatrists (O.R., G.S., and N.B.) on the first day of admission. Patients in the state of alcohol withdrawal received benzodiazepine therapy to alleviate withdrawal symptoms. The duration of alcohol withdrawal as estimated by the treating psychiatrists was on average 2–4 days after admission. The control group consisted of 50 healthy volunteers recruited through local advertisements at the MHRI and Siberian State Medical University. Healthy individuals were screened using a self-report questionnaire. The questionnaire screens for both physical and mental pathology, e.g. endocrine, neurological, gynaecological and psychiatric disorders.

Measurements

Phenotype measures

Depressive symptoms were assessed using the 17 item Hamilton Depression Rating Scale (HAMD-17). Anxiety

Table 1. Demographics and clinical characteristics of the study population.

Indicators	MD ($n = 43$)	AUD ($n = 42$)	AUD + MD ($n = 44$)	Healthy controls ($n = 50$)	p Value
Age, Me (Q1; Q3) years	51 (36; 58)	44.5 (39.75; 54)	45 (37.25; 49)	42 (35; 52.25)	0.192 (Kruskal-Wallis test)
Gender (Male, n (%) / Female, n (%))	11 (25.6%) / 32 (74.4%)	34 (81%) / 8 (19%)	29 (65.9%) / 15 (34.1%)	20 (40%) / 30 (60%)	**0.0001** (Kruskal-Wallis test)
Duration of disease, Me (Q1; Q3) years					
MD	4 (2; 9.5)	–	5.0 (2.0; 12.0)	–	0.507 (Mann-Whitney test)
AUD	–	17.0 (10.0; 24.0)	13.0 (8; 20.0)	–	0.144 (Mann-Whitney test)
Severity of Symptoms					
HAMD-17	23 (18; 26)	–	20 (17.25; 26)	–	0.300 (Mann–Whitney test)
HARS	20 (13; 27)	–	20 (17; 26.5)	–	0.855 (Mann–Whitney test)
AUDIT	–	25 (18.75; 32)	27 (20; 29.75)	–	0.822 (Mann–Whitney test)
OCDS	–	34.5 (23; 45.25)	33.5 (22.25; 41)	–	0.424 (Mann–Whitney test)
SHAPS	1 (0; 4)	1 (0; 3)	2 (0; 3.5)	–	0.471 (Kruskal–Wallis test)
SASS	33 (28; 37)	36.5 (34; 40.75)	34 (29.75; 38.5)	–	0.061 (Kruskal–Wallis test)

In bold: significant difference, p-value <0.05
Me (Q1; Q3): median (lower quartile; upper quartile)
MD: mood disorder; AUD: alcohol use disorder; HAMD-17: 17 item Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Scale; AUDIT: Alcohol Use Disorders Identification Test Consumption; OCDS: Obsessive Compulsive Drinking Scale; SHAPS: Snaith-Hamilton Pleasure Scale; SASS: Social Adaptation Self-evaluation Scale

symptoms were measured using the Hamilton Anxiety Scale (HARS). Anhedonia, a core symptom of depression and addiction, was measured using the Snaith-Hamilton Pleasure Scale (SHAPS). Alcohol use and dependency were measured with the Alcohol Use Disorders Identification Test (AUDIT). Craving was assessed using the Obsessive Compulsive Drinking Scale (OCDS). The Social Adaptation Self-evaluation Scale (SASS) was used to measure the level of social adaptation. We used common Russian translations of the originals (verified by back translation into English) (see Levchuk et al. 2020 for more details). The psychometric tests were performed during the first week of admission, after remission of withdrawal or intoxication symptoms.

Biomarkers

Peripheral venous blood was collected from each subject at 8.00–9.00 a.m. on the morning after hospital admission, after eight hours of overnight fasting before intake of any food or medication. Blood was sampled in BD Vacutainer tubes with coagulation activator and centrifuged at 2000 rcf at 4 °C for 20 min. Serum samples were stored at −80 °C until analysed. Concentrations of cytokines were determined on the MAGPIX multiplex analyser (Luminex, Austin, Texas, USA) using xMAP® Technology based on the Core Facility «Medical genomics», Tomsk NRMC. Panel HCYTMAG-60K-PX41 by MILLIPLEX® MAP (Merck, Darmstadt, Germany) was used to determine the levels of the markers. The detected information is processed by special Luminex xPONENT® software, with subsequent export of data to the MILLIPLEX® Analyst 5.1 program. For a list of the cytokines measured and the abbreviations used, see Supplementary Table 1.

Statistical analysis

Data analysis was carried out using SPSS Statistics software (version 23) for Windows. The Shapiro-Wilk test was used to determine if the data followed a normal distribution. Nonparametric Kruskal-Wallis and Mann-Whitney U-tests were used to assess the significance of intergroup differences. The Chi-square test was used to analyse the categorical variables. Statistically significant differences were considered p-values less than 0.05. Bonferroni correction was used for multiple comparisons.

Results

Demographics and clinical characteristics of the study population

The demographics and clinical characteristics of the study population are summarised in Tables 1 and 2. In the groups of MD and healthy individuals, the majority were women ($p = 0.0001$ and $p = 0.0001$ respectively compared with AUD group; $p = 0.0001$ and $p = 0.048$ respectively compared with AUD + MD group). The depression subtype significantly differed between MD as comorbidity of AUD in comparison to the group of MD only patients for Depressive Episode (F32) and Dysthymia (F34.1).

The cytokine levels in the entire study population

The cytokine levels as measured in the study population are shown in Table 3.

In MD group we found increased IFN-2α ($p = 0.0001$), IL-6 ($p = 0.004$), IL-7 ($p = 0.0001$) levels, and decreased IL-1β ($p = 0.017$) and TNFα ($p = 0.0001$)

levels in comparison to those in healthy controls. The level of anti-inflammatory cytokines (IL-1RA and IL-10) was lower than that in healthy individuals ($p = 0.0001$; $p = 0.001$ respectively).

Patients with AUD showed an elevated level of IFN-2α ($p = 0.0001$), IL-2 ($p = 0.016$), IL-7 ($p = 0.0001$), IL-8 (p=0.0001) and IL-4 (p=0.0001) and decreased level of IL-12p40 ($p = 0.004$) and IL-1RA (p=0.008) compared with healthy individuals.

MD + AUD group demonstrated an increase in IFN-2α ($p = 0.0001$) and IL-8 ($p = 0.012$) levels against the background of a decrease in IL-1RA ($p = 0.0001$) and IL-10 ($p = 0.019$) in comparison to healthy persons.

Serum cytokine levels in MD and comorbidity MD + AUD

In MD group we found increased IL-6 ($p = 0.001$), IL-7 ($p = 0.001$) and IL-13 ($p = 0.006$) levels, and decreased TNFα (p=0.0001), IL-1RA ($p = 0.012$), IL-10 ($p = 0.002$) compared with group MD + AUD (Figure 1).

Serum cytokine levels in AUD and comorbidity MD + AUD

Patients with AUD showed elevated levels of IL-1β ($p = 0.046$), IL-2 ($p = 0.004$), IL-7 ($p = 0.0001$), IL-4 ($p = 0.049$) and IL-13 ($p = 0.015$) in contrast with MD + AUD group (Figure 2).

Correlation of cytokine levels with psychometric measures

Spearman's correlation analyses were provided between the cytokine levels and psychometric measures (HAMD-17, HARS, SHAPS, AUDIT-C, OCDS and SASS) in the three groups. The results are given in Supplementary Table 2.

Discussion

The present study examined cytokine levels in the serum of newly admitted patients with MD and AUD in comparison to their levels in persons with comorbidity MD + AUD and in healthy individuals. The serum levels of fifteen cytokines (11 pro-inflammatory and 4 anti-inflammatory) were measured in the morning after admission in fasting state and before the start of

Table 2. Nosological structure of MD in the study groups.

Diagnosis (ICD-10)	MD ($n = 42$)	AUD + MD ($n = 44$)
Bipolar Affective Disorder (F31)	2.3% ($n = 1$)	18.2% ($n = 8$)
Depressive Episode (F32)	46.5% ($n = 20$)*	18.2% ($n = 8$)
Recurrent Depressive Disorder (F33)	32.6% ($n = 14$)	27.3% ($n = 12$)
Dysthymia (F34.1)	18.6% ($n = 8$)	36.4% ($n = 16$)*

Note: In the case of dysthymia, only the current symptomatology was considered regardless of the duration of its existence. *$p = 0.043$ (chi-square test)

Table 3. The cytokine levels in study population.

Indicators	MD ($n = 43$)	AUD ($n = 42$)	AUD + MD ($n = 44$)	Healthy controls ($n = 50$)	p Value (Kruskal-Wallis test)
Pro-inflammatory cytokines					
IFN-2α	63.24 (38.93–99.17)	98.42 (57.92–144)	73.62 (30.39–148.57)	23.70 (17.00–38.77)	**0.0001**
	$p = 0.0001$	**$p = 0.0001$**	**$p = 0.0001$**		
IFN-γ	11.08 (4.46–24.74)	12.87 (6.79–20.48)	13.73 (5.59–19.54)	9.47 (7.37–13.56)	0.727
IL-1α	114.92 (39.27–410.06)	73.79 (36.9–102.96)	81.56 (34.36–143.18)	58.79 (50.45–70.24)	0.183
IL-1β	1.45 (0.51-2.03)	2.91 (1.2–4.47)	1.22 (0.55–3.97)	2.46 (1.44–3.12)	**0.022**
	$p = 0.017$				
IL-2	4.18 (2.79–6.58)	10.98 (5.25–15.25)	1.46 (0.56–13.06)	5.15 (4.28–7.82)	**0.001**
		$p = 0.016$			
IL-6	43.81 (9.35–121.2)	7.58 (3.7–26.65)	4.81 (2.08–8.12)	5.18 (3.80–7.89)	**0.001**
	$p = 0.004$				
IL-7	27.70 (20.14–46.7)	32.75 (29.22–41.36)	11.88 (9.31–31.97)	11.69 (9.03–17.18)	**0.0001**
	$p = 0.0001$	**$p = 0.0001$**			
IL-8	10.51 (5.98–24.25)	22.86 (15.46–42.44)	19.06 (7.98–38.52)	10.32 (5.65–18.48)	**0.0001**
		$p = 0.0001$	**$p = 0.012$**		
IL-12p40	17.18 (5.56–54.58)	24.16 (11.49–43.32)	28.87 (18.99–45.25)	42.10 (26.87–46.06)	**0.007**
		$p = 0.004$			
IL-17A	4.02 (2.1–9.91)	6.21 (2.17–8.72)	5.82 (2.41–8.55)	4.61 (3.43–7.48)	0.952
TNFα	5.9 (3.78-8.4)	14.04 (10.29–20.48)	12.60 (8.57–19.59)	15.13 (8.41–20.63)	**0.0001**
	$p = 0.0001$				
Anti-inflammatory cytokines					
IL-1RA	12.31 (6.6–17.5)	19.47 (10.87–40.14)	16.35 (11.15–29.26)	41.86 (32.26–53.87)	**0.000**
	$p = 0.0001$	**$p = 0.008$**	**$p = 0.0001$**		
IL-4	80.95 (34.62–129.28)	178.34 (119.09–304.94)	103.03 (21.88–323.81)	86.31 (65.23–105.63)	**0.000**
		$p = 0.0001$			
IL-10	2.55 (1.21–3.24)	7.51 (2.59–11.11)	5.26 (1.66–10.74)	6.46 (3.96–8.31)	**0.003**
	$p = 0.001$		**$p = 0.019$**		
IL-13	26.79 (9.13–122.74)	19.04 (9.52–32.78)	10.21 (2.16–22.05)	13.30 (9.77–17.47)	**0.010**

In bold within group columns: significant p-value of comparison with healthy control group (Mann–Whitney U-test with Bonferroni correction)

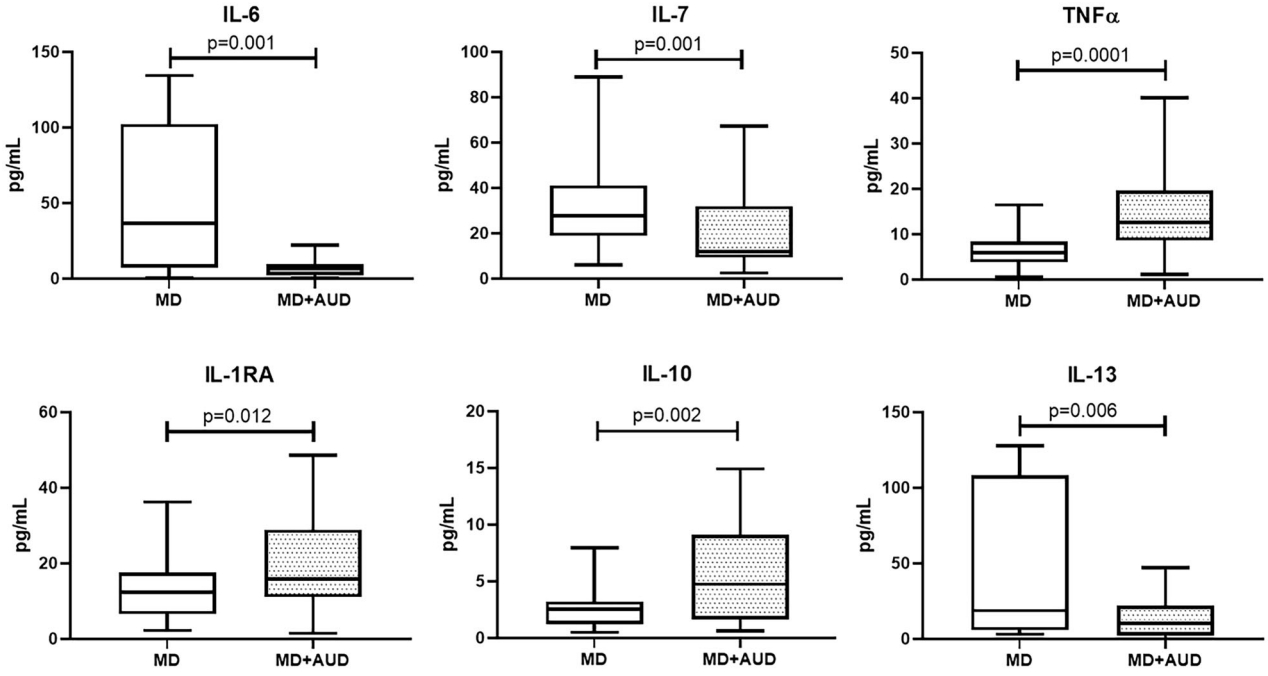

Figure 1. Serum Cytokine Levels in patients with MD and comorbidity MD + AUD. Mann–Whitney *U*-test with Bonferroni correction.

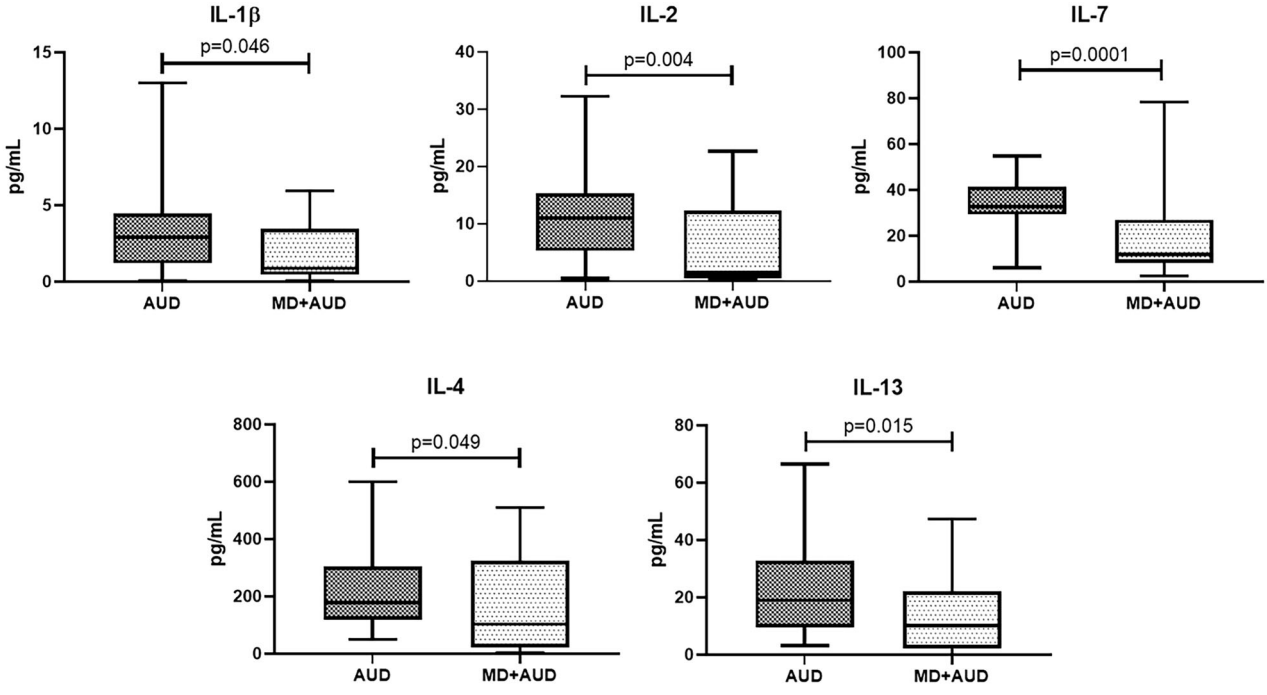

Figure 2. Serum Cytokine Levels in patients with AUD and comorbidity MD + AUD. Mann–Whitney *U*-test with Bonferroni correction.

any medication. For 8 of the 11 pro-inflammatory and for all 4 anti-inflammatory cytokines, significant differences existed between the levels measured in members of the four groups of individuals. Most consistent were the increase in IFN-2α and the decrease in IL-1RA in patients compared to healthy volunteers. The levels of IL-7 and IL-13 were significantly higher in both patients with pure AUD and those with pure MD compared to patients with a combination of both. There was no significant correlation between the levels of any of the cytokines measured and the duration of AUD illness.

Demographics and baseline parameters

There were significantly more women in the MD group than in the groups AUD and MD + AUD. These differences are consistent with literature data. Adult women are about twice as likely to be diagnosed with major depression as men (Kessler 2003) and the gender difference continues in subjects of 60 year and older (Girgus et al. 2017). In this meta-analysis of Girgus et al. (2017), a small but significant difference in symptomatology between male and female depressed patients became evident. Men with depression were more likely to report alcohol/drug abuse and risk taking/poor impulse control, while depressed women reported more intensely depressed mood, appetite disturbance/weight change, and sleep disorders (Cavanagh et al. 2017). The large number of men in the group comorbidity MD + AUD is explained by the fact that patients were predominantly recruited from the department of addictive disorders. Relevant gender differences were also observed in a longitudinal study of 12–21 year old scholars (Marmorstein 2009). The largest association has been found between alcohol use and symptoms of depression in adolescent girls, but gender inequality decreases with age and levels off in adulthood. Evidence suggests that AUD increases the risk of MD, rather than vice versa which is probably attributable to pharmacological and metabolic changes as a result of long-term alcohol exposure (Boden and Fergusson 2011). In our study, dysthymia was the most common MD associated with AUD. However, among individuals of an European population with AUD, nearly 33% met the criteria for major depressive disorder, and only 11% - dysthymia (Grant et al. 2004; McHugh and Weiss 2019). However, in the aforementioned study, meeting during the preceding 12 months the criteria of the fourth edition of the diagnostic and statistical manual of mental disorders (DSM-IV) (American Psychiatric Association 1994) is applied much more strictly, resulting in a much lower prevalence of dysthymia than in our case. In addition, the ICD-10 diagnostic criteria for dysthymia may allow including probable cases of "double depression", when dysthymia was in fact a manifestation of "underrecovery" from a previous depressive episode.

Cytokines in MD

In MD patients, several pro-inflammatory cytokines were higher (IFN-2α, IL-6 and IL-7) or lower (IL-1β and TNFα) than in the control group. At the same time, the level of anti-inflammatory cytokines such as IL-1RA were reduced compared to healthy individuals. The imbalance between pro- and anti-inflammatory cytokines in patients with depressive disorder is supported by the results of other studies (Song et al. 2009; Pandey et al. 2018). In the meta-analysis of Dowlati et al. (2010) who included data from 24 studies measuring TNFα, IL-1β, IL-6, IL-4, IL-2, IL-8, IL-10, and IFN-γ in patients with major depression, only the levels of TNFα and IL-6 were significantly higher in depressed subjects in comparison to healthy control subjects. However, in a more recent meta-analysis of 82 studies by Köhler et al. (2017) the peripheral levels of IL-6, TNFα, IL-10, IL-13, and IL-1RA were significantly higher in depressed patients in comparison to healthy individuals, while the levels of IL-1β, and transforming growth factor-beta 1 were not significantly different. Another meta-analysis showed that treatment with antidepressants significantly reduced TNFα levels only in responders, and that responders had significantly lower TNFα levels than nonresponders (Liu et al. 2020). For an overview of the various findings, please refer to Petralia et al. (2020). We should definitely consider that our results may be biased by the nosological heterogeneity of our MD patient population. IL-1β has been considered as a marker of resistant depression (Uint et al. 2019), the decrease in this cytokine in our study may be due to the fact that almost all patients responded well to therapy. In the development of depression, a role has recently been attributed to activation of both the inflammatory response system (IRS) and the Compensatory Immune Response System (CIRS) (Debnath et al. 2021). Here, an important role must be assigned to neuroglia (Jia et al. 2021), which, incidentally, is probably mediated in part through astrocytes (Dossi et al. 2018; Petralia et al. 2020; Jia et al. 2021).

Cytokines in AUD

In our patients with AUD, we measured significantly elevated levels of IFN-2α, IL-2 IL-7, IL-8 and IL-4 and decreased levels of IL-12p40 and IL-1RA in comparison to the levels in healthy individuals. Although the elevated levels of pro-inflammatory cytokines TNFα and IL-6 had a particularly large effect size in such patient groups (next to IL-7 and IL-8) (Adams et al. 2020), we did not observe significant differences for these cytokines between subjects with AUD and healthy persons. The relationship between the use of alcohol in AUD and activation of the immune system is rather complex as alcohol has several peripheral effects that may play a role. This may include influencing the intestinal

epithelium to increase permeability to bacterial products, which may then penetrate into the general circulation (Leclercq et al. 2014). In addition, alcohol has toxic effects in various organ systems (liver, heart, lungs) where the cellular damage may result in immune activation, which incidentally may itself also be a mechanism of the damage (Crews et al. 2006; Fujimoto et al. 2000). In addition, alcohol has an acute effect on the levels of interleukins (increase IL-8 and decrease TNFα) (Hillmer et al. 2020). In experiments in mice, it has been demonstrated that alcohol consumption contributes to a decrease in proinflammatory function (Starkenburg et al. 2001) and this does correlate with the higher risk of infection of people with AUD (Szabo and Mandrekar 2009). Altogether, many possibilities exist for a peripheral mechanism for the cytokine changes in AUD, which may obscure a possible cerebral component.

Cytokines in MD + AUD

Patients in the MD + AUD group demonstrated elevated IFN-2α and IL-8 levels and decreased IL-1RA and IL-10 levels in comparison to healthy individuals. In hepatitis C patients, treatment with IFN-2α often leads to the development of depression (Udina et al. 2012; Machado et al. 2017). The mechanism is not entirely known, but has often been associated with impaired serotonergic neurotransmission (Schaefer et al. 2003; Prather et al. 2009; Hoyo-Becerra et al. 2014). The prophylactic efficacy of selective serotonin reuptake inhibitors (SSRIs) has been sufficiently proven (Baraldi et al. 2012; Jiang et al. 2014; Ehret and Sobieraj 2014; Sarkar and Schaefer 2014). In any case, it has been found that depression due to treatment with INFα is primarily related to biological factors and less or not psychological factors related to neuroticisms (Małyszczak et al. 2019). IL-6 also appears to play a role in susceptibility to IFNα-induced depression (Cassidy et al. 2002; Prather et al. 2009; Udina et al. 2012; Machado et al. 2017). In alcohol-dependent-subjects IL-10 level was negatively associated with depression, anxiety and alcohol-craving (Leclercq et al. 2012).

In our study patients with MD + AUD showed a decreased level of IL-1, IL-2, IL-7, IL-4 and IL-13 in comparison to the AUD group (Figure 2). These findings differ from those of Neupane and colleagues (Neupane et al. 2014) who found higher levels of the IL-6, TNF and IFN-γ in Nepalese AUD patients with (a history of) MD than individuals without MD. Because the differences were greatest in individuals who drank little, these authors suggest that frequent and intense drinking may attenuate the difference. This may also be a reason for the discrepancy with our results. This fact may also explain the previously mentioned not increased levels of TNFα and IL-6 in our population with AUD.

In the study of Archer et al. (2019) patients with major depressive disorder (MDD) and AUD showed higher levels of IL-6, IL-8, high sensitivity C-reactive protein (hs-CRP), and Chitinase-3-like protein 1 (YKL-40 or CHI3L1), than in MDD patients without AUD. We obtained opposite results for IL-6, but used an entirely different design. In our study we found increased IL-6, IL-7 and IL-13 levels, and decreased TNFα, IL-1RA and IL-10 levels in the MD group in comparison to the MD + AUD group (Figure 1).

Possible involvement of dorsal diencephalic connection system (habenula)

In recent years we have become very interested in the possible role of the evolutionarily very old dorsal diencephalic connection (DDC) system that allows the forebrain to influence the midbrain via the habenuloid complex (Loonen and Ivanova 2018). The habenula's connections, well preserved during evolution, to the dopaminergic, serotonergic, and (indirectly) adrenergic centres in the midbrain regulate the activity of these ascending monoaminergic pathways and thus play an important role in depression and addiction (Loonen and Ivanova 2016b; Batalla et al. 2017). Within this system, the interaction between microglia, astrocytes and neurons may play an important role (Zhao et al. 2018; Guan et al. 2020). It has been suggested that the release of cytokines from microglia and other immunocompetent cells in the lateral habenula results in remodelling of the extracellular matrix – and therefore modulating the function – of this structure (Ito et al. 2021). The majority of the habenuloid output of the habenula to the midbrain is glutamatergic, either primary or as a co-transmitter with, for example, acetylcholine (Antolin-Fontes et al. 2015). It is tempting to speculate about what role matrix changes might play in bringing about a shift in the neurotransmitter output of the habenula.

Possible future avenues of cytokines study

Given the undoubted role of immune system dysregulation in the pathophysiology of affective disorders and addictions, we suggest the need for an integrated approach to study the mechanisms of the influence of alcohol on mood disorders. Genes encoding cytokines

are highly polymorphic and data on the existence of a genetic profile associated with pro-inflammatory cytokines in patients suffering from mood disorders and genes involved in innate immunity in addicted people are described (Clerici et al. 2009; Crews 2012). Stress events are also associated with activation of the inflammatory immune system as well as changes in inflammatory cytokines in the brain (Audet et al. 2014). Transcriptome profiling enables has revealed involvement of the brain's neuroimmune system in regulating alcohol abuse and dependence as well as psychiatric disorders (Warden et al. 2016; Chen et al. 2022). Combining the results of studies of the above approaches with the measurement of the serum cytokine profile and immunophenotyping, in our opinion, may be promising in further studies. At the same time, complex research requires more serious approaches to data processing. Modern deep and machine learning methods can help interpret complex relationships between clinical and biological parameters (Durstewitz et al. 2019). For example, the new nomothetic network psychiatry approach, which uses machine learning methods to build data-driven causal models of mental illness by assembling risk-resilience, adverse outcome pathways, cognitome, brainome, staging, symptomatome, and phenomenome latent scores in a causal model (Stoyanov and Maes 2021).

Given the wide variability in cytokine levels from various external and internal factors, it is promising to comprehensively study the genetic, transcriptomic and proteomic information related to cytokines. Also, future lines of research should focus on the application of sophisticated analysis methods such as machine learning and deep learning to understand the complex mechanisms of interaction between psychiatric diseases and the immune system.

Limitations

The main limitations of our research are the discrepancy between the studied groups in terms of gender and structure of MD. However, since our study design was cross-sectional, this reflects clinical reality. It seems inappropriate to us to stratify for gender or diagnostic category of mood disorders in an exploratory study, as there may be an interaction between these variables and possibly causal activation of the immune system. Another important limitation of our study is that our findings regarding TNFα and IL-6 in individuals with AUD are not consistent with literature data.

Conclusion

Although both depressive mood disorders and alcohol-related disorders involve changes within the immune system, it is extremely difficult to get a grip on the biological mechanisms involved. Because alcohol exhibits a broad palette of cerebral and peripheral effects, it is difficult to work out how changes in serum levels of cytokines relate to the biological changes that determine how alcohol causes mental disorders characterised by mood change or alcohol-seeking behaviour. Therefore, even with our study, we cannot reach unequivocal conclusions. Hence, in our opinion, it is better to focus this type of research on a well-established influence of certain cytokines on the functioning of specific intracerebral circuits found in other types of research. Promising, in our opinion, is a comprehensive assessment of the dysregulation of the immune system in affective and addictive diseases using machine and deep learning methods. We do think that our findings, together with the results of others, may provide an impetus to look with greater emphasis at the interaction of the immune system with the functioning of the basic behavioural regulatory dorsal diencephalic connection system. Then the results of our study can be reinterpreted and more successfully.

Acknowledgements

Dutch universities have suspended all forms of cooperation with Russian educational and research institutions due to the conflict with Russia over Ukraine. The Board of the Faculty of Science and Engineering of the University of Groningen exempted the manuscript of this article because the data collection was already completed and the results were described in this manuscript.

Disclosure statement

The authors report there are no competing interests to declare. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Funding

This research was funded by a grant from the Russian Science Foundation [project No. 19-15-00023].

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Data availability statement

The datasets generated for this study will not be made publicly available, but they are available on reasonable request to Svetlana A. Ivanova (ivanovaniipz@gmail.com), following approval of the Board of Directors of the MHRI, in line with local guidelines and regulations.

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