Nordic Journal of Psychiatry

ISSN: 0803-9488 (Print) 1502-4725 (Online) Journal homepage: http://www.tandfonline.com/loi/ipsc20

Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls

Nina Groven, Egil A. Fors, Valentina C. Iversen, Linda R. White & Solveig Klæbo Reitan

To cite this article: Nina Groven, Egil A. Fors, Valentina C. Iversen, Linda R. White & Solveig Klæbo Reitan (2018): Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls, Nordic Journal of Psychiatry, DOI: 10.1080/08039488.2018.1493747

To link to this article: https://doi.org/10.1080/08039488.2018.1493747

Published online: 31 Jul 2018.

NORDIC JOURNAL OF PSYCHIATRY
https://doi.org/10.1080/08039488.2018.1493747

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls

Nina Groven[a], Egil A. Fors[b], Valentina C. Iversen[a,c], Linda R. White[d,e] and Solveig Klæbo Reitan[a,f]

[a]Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [b]General Practice Research Unit, Department of Public Health Sciences and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [c]Department of Tiller DPS, St. Olav's University Hospital, Trondheim, Norway; [d]Department of Neurology, St. Olav's Hospital, Trondheim, Norway; [e]Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [f]Department of Psychiatry, St. Olav's Hospital, Trondheim, Norway

ABSTRACT

Purpose: The reports regarding the status of the immune system in patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) have been inconclusive. We approached this question by comparing a strictly defined group of CFS/ME outpatients to healthy control individuals, and thereafter studied cytokines in subgroups with various psychiatric symptoms.

Materials and methods: Twenty patients diagnosed with CFS/ME according to the Fukuda criteria and 20 age- and sex-matched healthy controls were enrolled in the study. Plasma was analysed by ELISA for levels of the cytokines TNF-α, IL-4, IL-6 and IL-10. Participants also answered questionnaires regarding health in general, and psychiatric symptoms in detail.

Results: Increased plasma levels of TNF-α in CFS/ME patients almost reached significance compared to healthy controls ($p = .056$). When studying the CFS/ME and control groups separately, there was a significant correlation between TNF-α and The Hospital Anxiety and Depression Scale (HADS) depressive symptoms in controls only, not in the CFS/ME group. A correlation between IL-10 and psychoticism was found in both groups, whereas the correlation for somatisation was seen only in the CFS/ME group. When looking at the total population, there was a significant correlation between TNF-α and both the HADS depressive symptoms and the SCL-90-R cluster somatisation. Also, there was a significant association between IL-10 and the SCL-90-R cluster somatisation when analyzing the cohort (patients and controls together).

Conclusions: These findings indicate that immune activity in CFS/ME patients deviates from that of healthy controls, which implies potential pathogenic mechanisms and possible therapeutic approaches to CFS/ME. More comprehensive studies should be carried out on defined CFS/ME subgroups.

ARTICLE HISTORY
Received 2 August 2017
Revised 24 May 2018
Accepted 21 June 2018

KEYWORDS
Immunopsychiatry; cytokines; chronic fatigue syndrome; depression; inflammation; psychiatry

Introduction

There is a lack of consensus in defining a homogenous patient group suffering from chronic fatigue syndrome/myalgic encephalopathy (consistently referred to CFS/ME in this article) [1]. The etiology is not understood and there is no consensus on treatment. CFS/ME affects 0.4–2.4% of young people, depending on whether 'chronic' is referred to 3 or 6 months, respectively [2], with substantial social and economic consequences for the individual as well as society. The prevalence of CFS/ME according to the Fukuda criteria [3] is estimated to be around 1% (0.1–6.4%) of the general population [1,4] with a majority of women affected (78%) [5]. Various pathogenic mechanisms have been proposed earlier [6].

Several groups have reported elevated plasma levels of proinflammatory cytokines such as IL-1, IL-6 and TNF-α as well as neopterin in patients with CFS/ME [7,8]. Attenuation of Th1 and Th17 and an increase in Th2 cytokines in CFS/ME [9] have been reported. One study has suggested that a shift towards Th2 responses seemed to be linked to a poorer psychiatric status in these patients [10]. ter Wolbeek et al. [11] showed that different scores of fatigue over time of adolescent girls were inversely correlated with the levels of IL-6 and TNF-α. Buchwald et al. [12] found that a febrile CFS/ME subgroup had elevated levels of IL-6. Pain is a common complaint and is an important factor in the Fukuda diagnostic criteria for CFS/ME [3]. Cytokines such as IL-6 are associated with peripheral pain sensory neurons [13], and TNF-α is suggested to play a role in central sensitisation of pain [14]. Others have published negative studies on cytokines in CFS [15]. This deviating picture may reflect that different subgroups of CFS/ME patients have been investigated.

Overall, there is considerable evidence that abnormalities of the immune system are involved in the pathogenesis of

CONTACT Nina Groven nina.groven@ntnu.no Department of Mental Health, Faculty of Medicine and Health Sciences, NTNU, PO Box 8905 MTFS, NO-7491 Trondheim, Norway

CFS/ME [16], a finding that might be employed for treatment once more systematic knowledge of the condition has been established. The association between inflammation and depression has been well established [17,18]. Although serious psychiatric morbidity is excluded in CFS/ME, there are reports of subclinical depression and immune system involvement in this patient group [19]. The objective of this study was to look for deviations of the immune system/cytokines related to subclinical psychiatric symptoms in CFS/ME.

Our aim was to study cytokine levels in a strictly defined female patient group aged 18–42 years, fulfilling the Fukuda diagnostic criteria for CFS/ME [3]. The levels of cytokines were correlated with scores in validated psychometric tests including psychiatric symptoms. Immune activity was assessed through the measurement of well-known cytokines representing both the Th1 and the Th2 arms of the immune system.

Materials and methods

Sample

Patients

The study population was part of a larger study where all general practitioners in central Norway (population 750,000) were encouraged to refer adult patients aged 18–60 years with fatigue of unknown etiology to the Multidisciplinary Pain Center at St. Olav's Hospital, Norway, for evaluation and treatment according to ordinary hospital routine. Participants were carefully evaluated by senior medical doctors, physiotherapists and psychologists according to the Fukuda criteria for CFS/ME [3]. They were obliged to have clinically evaluated, unexplained, persistent, or relapsing fatigue lasting more than 6 months. Pregnant patients and patients meeting the ACR criteria for fibromyalgia [20] were excluded.

Of the first 22 CFS/ME patients consecutively asked, 20 accepted (all female, aged 18–42 years), and were included in this study.

Healthy control individuals

Healthy controls were recruited by oral request and information to female students and staff aged 18–40 years at the Norwegian University of Science and Technology (NTNU), and St. Olav's Hospital. Exclusion criteria were pregnancy and any known diseases. For this study, 20 were recruited, all aged 20–40 years.

Study design and procedure

This is a small, non-randomized observational study ($N = 40$).

Questionnaires were sent by mail to all participants in the patient group. Patients completed questionnaires upon being diagnosed 0–8 weeks prior to the withdrawal of plasma. For the control group, questionnaires were completed and handed to the researcher the same day as blood was sampled. Data were collected during the period February 2011 to April 2011. No restrictions were given prior to the blood sampling.

Ethics

The study was part of a larger project (REK 4.2008.2586, Clinical trials identity number: NCT00920777) and was approved by the local Regional Committee for Medical and Health Research Ethics for including the control group (REK 2011/759). All participants provided written, informed consent.

Measurements

Questionnaires

The Hospital Anxiety and Depression Scale (HADS). HADS is a validated, self-complete scale [21,22] for monitoring depressive and anxiety symptoms. It is subdivided into HADS depression and HADS anxiety. The scores in both subdivisions range from 0 to 21 with high scores being suggestive of more symptoms. The total potential HADS score thus ranges from 0 to 42. In this study, we used HADS as a continuous variable.

The Chalder Fatigue Scale. The Chalder Fatigue Scale [23,24] consists of 11 items measuring fatigue. The total sum of each of the 11 items, scored on a 0–3 Likert scale and ranging from 0 to 33, was applied as a continuous variable; higher scores imply more severe fatigue.

Numeric Rating Scale (NRS). A NRS was used to evaluate the subjective feeling of experienced pain on average for the last week, and was taken from the Brief Pain Inventory [25,26]. NRS is a Likert scale ranging from 0 ('no pain') to 10 ('maximal possible pain,' i.e. a continuous variable).

The Symptom Checklist-90-Revised (SCL-90-R). SCL-90-R [27] is a 90-item, self-rating instrument for assessing psychopathology during the last week. It constitutes nine primary psychiatric symptom dimensions and three summary scores termed global scores. Each item is rated on a 5-point Likert scale ranging from 0 to 4.

Cytokines

Laboratory assays. Blood samples for cytokine analysis were collected in EDTA tubes. Blood samples were immediately placed in ice-water and centrifuged within 30 min (1500g, 10 min, 4 °C). Plasma was aliquoted into cryogenic vials and frozen at −80 °C until assayed.

ELISA kits from R&D Systems® were used to analyse plasma for IL-4 (Quantikine® HS, catalog number HS400; detection limit, 0.11 pg/mL; standardized for serum, but often used for plasma); IL-6 (Quantikine® HS, catalog number HS600B; detection limit, 0.039 pg/mL); TNF-α (Quantikine® HS, catalog number HSTA00D; detection limit, 0.106 pg/mL); and IFN-γ (Quantikine® HS, catalog number DIF50; detection limit, <8.0 pg/mL). In this study, plasma IFN-γ levels except for two individuals were below the detection limit for the ELISA. For IL-10, the ELISA kit from Invitrogen Corporation (catalog number KHC0101; detection limit, <1 pg/mL) was used. One of the plasma samples from a control had to be excluded for IL-10. The samples were run and analysed

Table 1. Differences in psychometric evaluation between the two groups.

Parameter	CFS/ME ($n = 20$)		Control ($n = 20$)		p Value
	Mean	SD	Mean	SD	
HADS total	11.65	6.48	3.85	2.01	.000**
HADS-A	5.80	3.81	3.20	1.94	.026*
HADS-D	5.85	4.32	0.65	0.99	.000**
SCL-90-R somatisation	1.41	0.65	0.25	0.37	.000**
SCL-90-R obsessive–compulsive	1.34	0.47	0.36	0.25	.000**
SCL-90-R interpersonal sensitivity	0.46	0.50	0.12	0.13	.010*
SCL-90-R depression	1.01	0.45	0.22	0.27	.000**
SCL-90-R anxiety	0.43	0.46	0.14	0.19	.016*
SCL-90-R hostility	0.37	0.34	0.09	0.13	.012*
SCL-90-R phobic anxiety	0.14	0.25	0.07	0.14	.627
SCL-90-R paranoid ideation	0.20	0.32	0.08	0.11	.444
SCL-90-R psychoticism	0.14	0.15	0.04	0.06	.012*
SCL-90-R additional items	1.07	0.58	0.25	0.25	.000**
SCL-90-R GSI	0.72	0.29	0.17	0.16	.000**
Fatigue score	25.45	5.10	10.90	3.71	.000**
NRS pain	4.32	1.60	1.00	1.17	.000**

Note. Mann–Whitney *U* tests. Fatigue score: Chalder Fatigue Scale; GSI: Global Severity Index; HADS: Hospital Anxiety and Depression Scale; NRS: Numeric Rating Scale; SCL-90-R: Symptom Checklist-90-Revised.
*$p \leq .05$; **$p < .001$.

Table 2. Differences in cytokines between the two groups.

Parameter	CFS/ME ($n = 20$)		Control ($n = 20$)		p Value
	Median	Range	Median	Range	
IL-4	0.04	0.05	0.04	0.08	.583
IL-6	0.69	12.68	0.65	1.66	.314
IL-10	0.93	1.27	1.05	4.78	.194
TNF-α	1.41	5.19	1.08	3.05	.056

Note. Mann–Whitney *U* tests. Cytokine concentrations are expressed in pg/mL. For IL-10 in the control group: $n = 19$.

according to the manufacturers' instructions. The Thermo Labsystem, Inc. Multiskan spectrophotometric microplate reader was used for optical reading. All samples were analysed within 6 months of collection.

Statistical analysis

IBM SPSS Statistics Version 21 was used to run all statistical tests. All variables were tested for normality, using the Kolmogorov–Smirnov test. Non-parametric tests were chosen because the samples were not normally distributed. For between-group comparisons, the Mann–Whitney *U* test was applied. Spearman's rho (ρ) was used to test the correlations. The levels of $p < .05$ were considered significant.

Results

A total of 20 consecutively asked eligible female CFS/ME patients and 20 healthy female controls were included. There were no differences in mean age between CFS/ME [29.0 (SD, 8.7)] and control [28.5 (SD, 5.5)] ($\chi^2 = 22.5$, $df = 21$, $p = .369$) individuals. In psychometric evaluation, the CFS/ME group had significantly more of all symptom clusters except paranoid ideation and phobic anxiety (Table 1). Also for fatigue (Chalder Fatigue Scale) and pain (NRS), the CFS/ME group scored significantly higher than the control group.

For both CFS/ME patients and controls, we found a significant correlation between different psychometric measures.

Table 3. Spearman's ρ correlations between cytokines and fatigue, pain and HADS.

Group	Parameter	Fatigue score	NRS pain	HADS total	HADS-A	HADS-D
Total sample	IL-4	.09	.07	.04	−.01	.11
	IL-6	.07	.14	−.10	−.07	−.08
	IL-10	−.09	−.06	−.20	−.12	−.22
	TNF-α	.21	.26	.36*	.12	.46**
Control	IL-4	.34	−.01	.27	.06	.35
	IL-6	−.25	−.18	−.14	−.02	−.33
	IL-10	.01	.24	0.00	.11	−.04
	TNF-α	−.19	.05	.37	.17	.58*
CFS/ME	IL-4	−.22	−.01	−.31	−.17	−.26
	IL-6	.12	.20	−.39	−.27	−.28
	IL-10	.20	.30	−.29	−.19	−.19
	TNF-α	.17	.05	−.01	−.18	.23

Note. Spearman's ρ are given. Cytokine concentrations are expressed in pg/mL. Fatigue score: Chalder Fatigue Scale; NRS: Numeric Rating Scale; HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS anxiety; HADS-D: HADS depression.
*$p \leq .05$; ** $p \leq .01$.

There were also correlations between several cytokines (data not shown).

At a 0.05 α level, there were no significant differences in cytokine levels between the CFS/ME group and the control group (Table 2). However, TNF-α showed a trend towards an increase in the CFS/ME group ($p = .056$).

Correlations between cytokines and symptoms (psychiatric symptoms, pain and fatigue) in the whole population group ($N = 40$) revealed significant correlations between TNF-α and HADS total score as well as HADS depression ($p = .021$ and $p = .003$, respectively) (Table 3). TNF-α also correlated with the SCL-90-R symptom cluster somatisation ($\rho = .32$, $p = .044$). IL-10 correlated with the SCL-90-R cluster psychoticism ($\rho = .35$, $p = .032$).

Analysing the patient and control groups separately showed a correlation between TNF-α and HADS depression only for the control group ($p = .007$), whereas it could not be seen for HADS total score. There were no significant correlations between cytokines and HADS parameters in the CFS/ME group (Table 3).

The SCL-90-R psychoticism cluster correlated significantly with IL-10 in both the control group ($\rho = .52$, $p = .023$) and the CFS/ME group ($\rho = .47$, $p = .045$). IL-10 also correlated with somatisation in the CFS/ME group ($\rho = .46$, $p = .047$).

Discussion

The patients with CFS/ME showed a trend towards increased plasma levels of TNF-α compared to healthy controls. The patients with CFS/ME also showed significantly higher scores on the Chalder Fatigue Scale, NRS pain and psychometric tests HADS and SCL-90 than sex- and age-matched controls. For the total population and for healthy controls, there was an association between TNF-α and HADS-scores; this was not seen in the CFS/ME group. An association between IL-10 and psychoticism was found in both groups, whereas a correlation for somatisation was seen only in the CFS/ME group.

As we were comparing a healthy group with a group of patients, the findings of increased scores on pain, fatigue and psychiatric symptoms is expected. Pain and fatigue are included in CFS/ME diagnoses. Though CFS/ME diagnoses

were set according to the Fukuda criteria excluding severe psychiatric morbidity, experienced subjective symptoms are possible. Sub-clinical depression [19,28] as well as phobia and panic [5] have been reported in CFS/ME.

When comparing the levels of cytokines between the two groups (CFS/ME and control), there was a trend to a higher level of TNF-α in the CFS/ME group ($p = .056$). This finding is in accordance with the reports from other groups [7,29]. There are also negative reports [15,30]. Different studies have employed slightly different study populations and other criteria for inclusion, which may explain this variation. Our results infer an immune deviation with increased levels of TNF-α in certain subgroups of CFS/ME.

TNF-α is a potent proinflammatory cytokine with a pivotal function in immune protection. However, it also causes general symptoms of illness (often referred to as 'sickness behaviour') seen in various disorders, e.g. malaise, anorexia, pain, fatigue and circulatory changes [31]. TNF-α also is involved in the pathogenesis of several inflammatory disorders and thus it is a useful target for therapy (e.g. anti-TNF mAbs in inflammatory disorders like inflammatory bowel disease and autoimmune arthritis). Increases in TNF-α have been found in depression, normalising upon recovery [17,32,33]. TNF-α thus may represent a link between – or common etiological factor behind – both psychiatric symptoms (e.g. depression) and pain and fatigue in CFS/ME.

As the finding of inflammation in CFS/ME patients is deviating in different reports, it is interesting to look at potential subgroups of CFS/ME defined by certain psychiatric symptoms. TNF-α was positively correlated to HADS depression in the total population and in the control group in line with other reports on depression and TNF-α [34]. There was, however, no correlation in CFS/ME. Elevation of TNF-α in the CFS/ME group thus may be related to an inflammatory condition in CFS/ME. It seems that TNF-α in CFS/ME is so strongly increased that an effect on level on TNF-α of depression is masked. This increase in TNF-α independent of depressive symptoms in CFS/ME should be further explored.

There also was a significant correlation between TNF-α and somatisation for the sample ($N = 40$), a finding that may be explained by the known effects of TNF-α on malaise and general somatic condition. Although somatisation was seen related to TNF-α in the whole cohort, this was not seen when analysing the different groups. This disappearance of significance when analysing different subgroups most likely is due to the low number of participants, i.e. lack of power.

In the CFS/ME group, somatisation was positively correlated to increased levels of IL-10. The explanation to this is not obvious and has not been reported before. As IL-10 is regarded as a Th2 cytokine, the finding does not fit with the finding of increased TNF-α (a Th1-cytokine). Though it may be speculated that this could represent an adjustment by the immune system to restore homeostasis as suggested by Bo et al. [35], the finding should be replicated before further speculations.

IL-10 was also significantly increased in correlation to the psychoticism cluster in SCL-90-R for the whole sample ($N = 39$) as well as for each subgroup. Interestingly, increased *ex vivo* IL-10 production has been described in lymphocytes from patients with schizophrenia [36]. IL-10 is characterised as a Th2 cytokine. Several groups have reported that Th2 cytokines like IL-4 are increased in patients with the psychotic disorder schizophrenia [37–39]. It has been suggested that IL-10 is involved in the development of schizophrenia in mouse models [40]. Our findings of the Th2 cytokine IL-10 in relation to psychoticism independent of CFS/ME is in line with this but the phenomenon should be further studied before any conclusions are drawn.

An important limitation to our study is the sample size. We do, however, think that the findings are interesting and intend to continue exploring the field with a larger sample. Some biochemical issues need to be mentioned. We have been studying cytokines in plasma, not cerebrospinal fluid. This is, however, established in the studies on immunopsychiatry and the interaction between the peripheral immune system and the brain is comprehensive [41]. We have tested only a limited number of cytokines. The tested cytokines are believed to cover both Th1 and Th2 arms. Future studies should include more cytokines than the five we have tested for here, as well as other markers such as kynurenine/quinolone and its metabolites to give a better picture of immune status.

Questionnaires and blood samples were not collected on the same day for the patient group, whereas this was done for the control group. Although health challenges in CFS/ME are expected to be rather stable over days and weeks, similar conditions in patient and control groups should be ensured in future studies. Blood was drawn at different times during working hours 0800–1600. Participants were not given instructions regarding fasting or exercise. Though no clear indications for diurnal variation in cytokines are known, this should also be improved in future studies. Information on medication and substance use in the groups were unfortunately not recorded, nor information on hereditary disease load. However, as a group, the CFS/ME patients used very little medication. Also, state of menstrual cycle was not recorded. Future studies should take all such aspects into consideration.

The main strength in our study is the strict diagnostic criteria excluding patients with other somatic or psychiatric sources of symptoms (such as fibromyalgia and other rheumatic disorders, major depression, psychosis, lupus erythematosus and multiple sclerosis). We studied a homogenous group regarding age and sex. Furthermore, inclusion of participants, sampling and handling of blood and laboratory analyses were carried out by a single researcher under supervision of experienced personnel, securing standardised procedures.

By taking psychiatric parameters into consideration when exploring immunological varieties in CFS/ME, more knowledge in the pathophysiology and therapeutic approaches for this disorder might be achieved.

Acknowledgements

The authors thank Sylvia Nome Kvam for her extensive laboratory work and expertise.

Disclosure statement

All the authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The ELISA kits were funded by St. Olav's University Hospital, Forensic Dept. Br⌀set, Centre for Research and Education in Forensic Psychiatry.

References

[1] Brurberg KG, Fonhus MS, Larun L, et al. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ Open. 2014;4(2):e003973.
[2] Crawley E. The epidemiology of chronic fatigue syndrome/myalgic encephalitis in children. Arch Dis Child. 2014;99(2):171–174.
[3] Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(2):953–959.
[4] Johnston S, Brenu EW, Staines DR, et al. The adoption of chronic fatigue syndrome/myalgic encephalomyelitis case definitions to assess prevalence: a systematic review. Ann Epidemiol. 2013;23(6):371–376.
[5] Lindal E, Stefansson JG, Bergmann S. The prevalence of chronic fatigue syndrome in Iceland – a national comparison by gender drawing on four different criteria. Nord J Psychiatry. 2002;56(4):273–277.
[6] Clauw DJ. Perspectives on fatigue from the study of chronic fatigue syndrome and related conditions. PM R. 2010;2(5):414–430.
[7] Maes M, Twisk FN, Kubera M, et al. Evidence for inflammation and activation of cell-mediated immunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): increased interleukin-1, tumor necrosis factor-α, PMN-elastase, lysozyme and neopterin. J Affect Disord. 2012;136(3):933–939.
[8] Fletcher MA, Zeng XR, Barnes Z, et al. Plasma cytokines in women with chronic fatigue syndrome. J Transl Med. 2009;7:96.
[9] Broderick G, Fuite J, Kreitz A, et al. A formal analysis of cytokine networks in chronic fatigue syndrome. Brain Behav Immun. 2010;24(7):1209–1217.
[10] Torres-Harding S, Sorenson M, Jason LA, et al. Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS). Bull IACFS ME. 2008;16(3):19–33.
[11] ter Wolbeek M, van Doornen LJ, Kavelaars A, et al. Longitudinal analysis of pro- and anti-inflammatory cytokine production in severely fatigued adolescents. Brain Behav Immun. 2007;21(8):1063–1074.
[12] Buchwald D, Wener MH, Pearlman T, et al. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. J Rheumatol. 1997;24(2):372–376.
[13] Andratsch M, Mair N, Constantin CE, et al. A key role for gp130 expressed on peripheral sensory nerves in pathological pain. J Neurosci. 2009;29(43):13473–13483. 28
[14] Uceyler N, Schafers M, Sommer C. Mode of action of cytokines on nociceptive neurons. Exp Brain Res. 2009;196(1):67–78.
[15] Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, et al. Postinfective fatigue syndrome is not associated with altered cytokine production. Clin Infect Dis. 2007;45(6):732–735.
[16] Morris G, Maes M. A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. Metab Brain Dis. 2013;28(4):523–540.
[17] Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446–457.
[18] Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017;71(8):574–580.
[19] Milrad SF, Hall DL, Jutagir DR, et al. Depression, evening salivary cortisol and inflammation in chronic fatigue syndrome: a psychoneuroendocrinological structural regression model. Int J Psychophysiol. 2018, doi:10.1016/j.ijpsycho.2017.09.009.
[20] Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33(2):160–172.
[21] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–370.
[22] Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69–77.
[23] Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147–153.
[24] Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res. 1998;45(1):53–65.
[25] Cleeland CS. Pain assessment in cancer. In: Osoba D, editor. Effect of cancer on quality of life. Boca Raton: CRC Press; 1991. p. 293–305.
[26] Klepstad P, Loge JH, Borchgrevink PC, et al. The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. J Pain Symptom Manage. 2002;24(5):517–525.
[27] Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatry. 1976;128:280–289.
[28] Nas K, Cevik R, Batum S, et al. Immunologic and psychosocial status in chronic fatigue syndrome. Bratisl Lek Listy. 2011;112(4):208–212.
[29] Moss RB, Mercandetti A, Vojdani A. TNF-alpha and chronic fatigue syndrome. J Clin Immunol. 1999;19(5):314–316.
[30] Wyller VB, Sorensen O, Sulheim D, et al. Plasma cytokine expression in adolescent chronic fatigue syndrome. Brain Behav Immun. 2015;46:80–86.
[31] Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46–56.
[32] Hestad KA, Tonseth S, Stoen CD, et al. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. J ECT. 2003;19(4):183–188.
[33] Dahl J, Ormstad H, Aass HC, et al. Recovery from major depressive disorder episode after non-pharmacological treatment is associated with normalized cytokine levels. Acta Psychiatr Scand. 2016;134(1):40–47.
[34] Hestad KA, Aukrust P, Tonseth S, et al. Depression has a strong relationship to alterations in the immune, endocrine and neural system. CPSR. 2009;5:287–297.
[35] Bo SH, Davidsen EM, Gulbrandsen P, et al. Cerebrospinal fluid cytokine levels in migraine, tension-type headache and cervicogenic headache. Cephalalgia. 2009;29(3):365–372.
[36] Rothermundt M, Arolt V, Weitzsch C, et al. Production of cytokines in acute schizophrenic psychosis. Biol Psychiatry. 1996;40(12):1294–1297.
[37] Borovcanin M, Jovanovic I, Radosavljevic G, et al. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. J Psychiatr Res. 2012;46(11):1421–1426.
[38] Simsek S, Yildirim V, Cim A, et al. Serum IL-4 and IL-10 levels correlate with the symptoms of the drug-naive adolescents with first episode, early onset schizophrenia. J Child Adolesc Psychopharmacol. 2016;26(8):721–726.
[39] Guo J, Liu C, Wang Y, et al. Role of T helper lymphokines in the immune-inflammatory pathophysiology of schizophrenia: systematic review and meta-analysis. Nordic Journal of Psychiatry. 2015;69(5):364–372.
[40] Meyer U, Feldon J, Schedlowski M, et al. Immunological stress at the maternal-foetal interface: a link between neurodevelopment and adult psychopathology. Brain Behav Immun. 2006;20(4):378–388.
[41] Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev. 2014;42:93–115.