

World Journal of *Psychiatry*

World J Psychiatr 2020 August 19; 10(8): 175-201



ORIGINAL ARTICLE**Basic Study**

- 175 Serum levels of chemokines in adolescents with major depression treated with fluoxetine
de la Peña FR, Cruz-Fuentes C, Palacios L, Girón-Pérez MI, Medina-Rivero E, Ponce-Regalado MD, Alvarez-Herrera S, Pérez-Sánchez G, Becerril-Villanueva E, Maldonado-García JL, Jiménez-Martínez MC, Pavón L

SYSTEMATIC REVIEWS

- 187 Dietary modification in the treatment of schizophrenia spectrum disorders: A systematic review
Aucoin M, LaChance L, Clouthier SN, Cooley K

ABOUT COVER

Editorial board member of *World Journal of Psychiatry*, Dr. Wang is an Associate Researcher at the School of Medicine, São Paulo University in São Paulo, Brazil. Having received his MD degree from the same institution in 1987, Dr. Wang commenced postgraduate training in the university's Department of Psychiatry, receiving his Master's degree in 1995 and PhD in 2003. Since 2007, he has mentored Master's and PhD students in the Department of Psychiatry and been involved in population-based epidemiological surveys on mental health at the Section of Psychiatric Epidemiology (LIM-23). Since 2016, he has been a collaborator of the Global Burden of Disease Initiative, under the auspice of Washington University in Seattle, WA, United States. His ongoing research interests involve the application of evidence-based medicine in mental health, particularly in association with non-communicable diseases. (L-Editor: Filipodia)

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rajesh R Tampi

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

August 19, 2020

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ONLINE SUBMISSION

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Basic Study

Serum levels of chemokines in adolescents with major depression treated with fluoxetine

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Sánchez G, Becerril-Villanueva E, Maldonado-García JL, Jiménez-Martínez MC, and Pavón L analyzed the results; All authors approved the final manuscript.

Supported by Secretaria de Ciencia, Tecnología e Innovación, No. 0048/2014

Institutional review board

statement: The study was reviewed and approved by the ethics committee of the Instituto Nacional de Psiquiatría “Ramón de la Fuente Muñiz” (México).

Conflict-of-interest statement: The authors report no conflicts of interest in relation to the topic of this study.

Data sharing statement: Data of the studies are not publicly available but might be shared upon request from the corresponding author.

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Manuscript source: Invited manuscript

Received: February 29, 2020

Peer-review started: February 29, 2020

First decision: April 29, 2020

Revised: May 31, 2020

Accepted: June 27, 2020

Article in press: June 27, 2020

Published online: August 19, 2020

P-Reviewer: Kotzaldidis GD

S-Editor: Yan JP

L-Editor: Filipodia

P-Editor: Liu JH

Abstract

BACKGROUND

Major depressive disorder (MDD) is a global health issue that affects 350 million people of all ages. Although between 2% and 5.6% of affected individuals are adolescents, research on young patients is limited. The inflammatory response contributes to the onset of depression, and in adult MDD patients, symptom severity has been linked to chemokine levels.

AIM

To determine the differences in circulatory levels of chemokines in healthy volunteers (HVs) and adolescents with MDD, and assess the changes induced by fluoxetine consume.

METHODS

The 22 adolescents with MDD were monitored during the first 8 wk of clinical follow-up and clinical psychiatric evaluation was done using the Hamilton depression rating scale (HDRS). The serum levels of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1 α , MIP-1 β , interleukin (IL)-8, interferon gamma-induced protein (IP)-10, and eotaxin were measured in patients and HVs.

RESULTS

In all cases, significant differences were detected in circulating chemokine levels between patients before treatment and HVs ($P < 0.0001$). All chemokines decreased at 4 wk, but only MCP-1 and IL-8 significantly differed ($P < 0.05$) between 0 wk and 4 wk. In the patients, all chemokines rose to their initial concentrations by 8 wk *vs* 0 wk, but only IP-10 did so significantly ($P < 0.05$). All patients experienced a significant decrease in HDRS scores at 4 wk ($P < 0.0001$) and 8 wk ($P < 0.0001$) compared with 0 wk.

CONCLUSION

Despite the consumption of fluoxetine, patients had significantly higher chemokine levels, even after considering the improvement in HDRS score. The high levels of eotaxin, IP-10, and IL-8 partially explain certain aspects that are affected in MDD such as cognition, memory, and learning.

Key words: Adolescents; Major depression; Chemokine; Fluoxetine; Interferon gamma-induced protein-10

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Core tip: Major depressive disorder affects 350 million persons, of whom approximately 6% are adolescents. This study determined the differences in circulatory levels of chemokines including eotaxin, interleukin-8, induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α , and macrophage inflammatory protein-1 β in healthy volunteers and adolescents with major depression. In addition, the changes induced by antidepressants consumed during 8 wk of clinical follow-up were assessed, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors, such as fluoxetine in adolescents. Our results showed significant elevation in serum chemokine levels in adolescents with major depression despite treatment with fluoxetine, and an improvement in scores on the Hamilton depression rating scale.

Citation: de la Peña FR, Cruz-Fuentes C, Palacios L, Girón-Pérez MI, Medina-Rivero E, Ponce-Regalado MD, Alvarez-Herrera S, Pérez-Sánchez G, Becerril-Villanueva E, Maldonado-García JL, Jiménez-Martínez MC, Pavón L. Serum levels of chemokines in adolescents with major depression treated with fluoxetine. *World J Psychiatr* 2020; 10(8): 175-186

URL: <https://www.wjgnet.com/2220-3206/full/v10/i8/175.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v10.i8.175>



INTRODUCTION

Major depressive disorder (MDD) is a significant international health problem affecting 350 million people of all ages globally^[1]. Studies worldwide have reported prevalence rates of depression between 2.8% and 5.6% in adolescents^[2], yet research on this clinical condition is limited. The depressive symptomatology in adolescents can be confused with other psychiatric disorders, in turn affecting the proper diagnosis and normal development of patients. MDD in adolescents is associated with several negative outcomes including other psychiatric disorders later in life, educational impairment, self-injury, and suicide^[2,3].

The inflammatory response contributes to the onset of depression, as demonstrated by several meta-analyses^[4,5]. Three pathways interacting with the central nervous system (CNS) have been described through the peripheral inflammatory response^[6,7]. The first are the inflammatory factors that directly diffuse into the brain through leakage of the blood-brain barrier; the second pathway is when circulatory inflammatory factors indirectly act to stimulate the secretion of central inflammatory factors through vagal afferent nerves; the last pathway is when CNS cells directly produce inflammatory molecules and express their receptors. The first two possible ways help explain that the peripheral administration of cytokines can produce depressive-like symptoms, while the third way suggests that high levels of cytokines in the CNS may be strongly associated with the development of MDD, and that the circulatory cytokines levels correlate with cytokine levels in the CNS^[8].

These findings have prompted interest in soluble inflammatory molecules, called chemokines^[9]. Chemokines are considered a subtype of cytokines based on their functions during inflammation, although they differ structurally from cytokines. Canonically, chemokines favor the migration of leukocytes towards inflamed tissues along a concentration gradient, modulating cellular inflammatory responses^[10]. In addition, clinical evidence has demonstrated that chemokines are produced by astrocytes, microglia, and neurons^[11]. Chemokines and their receptors have significant functions in the CNS, for example, in brain development, plasticity, cell-to-cell communication, neurotransmission, neuroendocrinology, inflammatory processes, and behavioral regulation^[9,12].

A wide range of chemokines have been implicated in the develop of depression and depression-like behavior^[9,12-15]. Vogelzangs *et al*^[16] reported an association between interleukin (IL)-8, monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase-2 serum levels and depressive symptom severity in 591 patients. Nevertheless, few studies have evaluated serum chemokine levels in adolescents with MDD before and during clinical follow-up. Therefore, these inflammatory molecules have been proposed to be biological markers of MDD by several groups^[17,18].

The objective of this work was to determine the differences in circulatory levels of eotaxin or C-C motif chemokine ligand 11 (CCL11), IL-8 or C-X-C motif chemokine ligand 8 (CXCL8), IP-10 or CXCL10, MCP-1 or CCL2, macrophage inflammatory protein (MIP)-1 α or CCL3, and MIP-1 β or CCL4 in healthy volunteers (HVs) and adolescents with MDD; and to assess the changes induced by antidepressants consumed during 8 wk of clinical follow-up, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs), as fluoxetine, in adolescents^[19].

MATERIALS AND METHODS

Participants

Patients: The Adolescent Clinic of Instituto Nacional de Psiquiatría “Ramón de Fuente,” Mexico City, assessed 337 individuals and recruited 22 Mexican patients who met the inclusion criteria from January 2006 to December 2008. The patients were men and women aged 14 to 19 years, who met the diagnostic criteria for MDD per the Diagnostic and Statistical Manual of Mental Disorders IV - text revision, and whose episodes at the moment of the study were moderate. They had no history of treatment for MDD with SSRIs, the duration of their depressive episodes was no longer than 2 years, and their minimum baseline score on the Hamilton depression rating scale (HDRS) was ≥ 14 .

All included participants received an explanation and signed informed consent forms to participate in this study (INPRF-2035). They were recruited per the clinical follow-up in the INPRF-2035 research protocol, as approved by the ethics committee of Instituto Nacional de Psiquiatría, “Ramón de la Fuente Muñiz” Mexico.

Healthy volunteers: Eighteen HVs were recruited from the general population between January 2006 and December 2008. Clinical parameters of HVs were within normal reference ranges (data not shown). The Mini International Neuropsychiatric Interview confirmed that HVs did not suffer from any mental disorder, and all had been free of any medication use by 3 wk before blood sampling. Demographic data of this group are shown in [Table 1](#).

Clinical procedures

Psychiatrists diagnosed all subjects, and the clinical status of adolescents with MDD was determined using the validated Spanish version of the 21-item HDRS-21. Patients were free of antidepressants by 3 wk before the study and signed written consent forms only after receiving a detailed explanation of the study aims. All participants were treated with SSRIs. At the screening visit, after being administered the HDRS test, each participant underwent a laboratory examination to rule out any medical illness. Participants were evaluated every month along with clinical follow-up by their psychiatrists, who applied the HDRS test. [Figure 1](#) represents a summary of the number of participants, the pharmacological treatment, and the changes to the protocol.

Drugs

Fluoxetine dose was 20 mg/d, which was established and adjusted by the psychiatrists. The medications used by patients were paid for by themselves.

Serum samples

Blood samples (10 mL) were collected by venipuncture from the cubital vein using Vacutainer® SST™ tubes with gel for serum separation (REF: 367988; BD Vacutainer System, Franklin Lakes, NJ, United States). Then samples were centrifuged immediately ($1.125 \times g$) at 4°C for 15 min to obtain serum. Serum samples were aliquoted and stored at -80°C until use.

Chemokine measurements in serum

The serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1 α , and MIP-1 β were measured in serum using the Bio-Plex Pro™ Human Cytokine 27-Plex Assay Kit per the manufacturer's instructions. Detection was performed using streptavidin-phycoerythrin and quantified on the Bio-Plex MAGPIX™ Multiplex Reader (Bio-Rad Laboratories Inc., Hercules, CA, United States). Chemokine concentrations were determined by interpolation using standard curves in Bio-Plex Manager™ (version 6.1; Bio-Rad Laboratories Inc.). The ranges of detection (pg/mL) reported by the manufacturer were as follows: Eotaxin: 2.1-24390, IL-8: 1.9-22233, IP-10: 3.0-34730, MCP-1: 2.0-23446, MIP-1 α : 1.5-1773, and MIP-1 β : 1.1-13533.

Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 6.00 for MAC OS X (GraphPad Software, La Jolla, CA, United States). Homogeneity of variance and normality tests were applied initially, followed by one-way analysis of variance with the Bonferroni *post hoc* test. All values were expressed as mean \pm standard deviation (SD). $P < 0.05$ was considered statistically significant.

RESULTS

Clinical parameters

Clinical and laboratory tests were performed in MDD adolescents and HVs in the clinical laboratory. The complete blood chemistry, blood count, complete urinalysis, and thyroid function test (T3, T4, and TSH) results were within normal reference value ranges. No differences between the groups were detected. [Table 1](#) shows their demographics and recurrence rates, while psychiatric scale scores are presented in [Table 2](#). At 0 wk, MDD patients had an HDRS score of 19.41 ± 4.72 points, compared with 9.13 ± 3.5 at 4 wk and 6.09 ± 2.4 at 8 wk.

Chemokines

The chemokine levels are shown in [Table 2](#).

Table 1 Demographics and episodic data of the study sample

	HVs, <i>n</i> = 18	Patients, <i>n</i> = 22
Age in yr	18.9 ± 1.2	17.1 ± 2.3
Gender, male/female	4/14	4/18
BMI in kg/m ²	23.2 ± 2.1	23.1 ± 2.1
Education in yr	12.9 ± 1.2	11.5 ± 2.6
Family history, yes/no	3/15	8/14
First episode	N/A	8
Recurrent episode	N/A	14

Values are presented as mean ± standard deviation. BMI: Body mass index; HVs: Healthy volunteers; N/A: Not applicable.

Table 2 Clinical psychiatric scores and serum chemokine levels in adolescents with major depressive disorder in 8 wk of selective serotonin reuptake inhibitor treatment

Chemokine serum levels, pg/mL	HVs	Adolescents with MDD			Post hoc statistical analysis		
	<i>n</i> = 18	0 wk, <i>n</i> = 22	4 wk, <i>n</i> = 22	8 wk, <i>n</i> = 22	0 wk vs HVs	4 wk vs 0 wk	8 wk vs 0 wk
MCP-1 or CCL2	48.1 ± 3.7	107.7 ± 31.0	89.8 ± 19.9	102.9 ± 14.0	^d <i>P</i> < 0.0001	^a <i>P</i> < 0.05	NS
MIP-1α or CCL3	5.4 ± 1.0	7.3 ± 1.4	6.7 ± 1.4	7.4 ± 1.0	^d <i>P</i> < 0.0001	NS	NS
MIP-1β or CCL4	204.7 ± 42.2	324.0 ± 61.5	311.8 ± 48.1	294.8 ± 34.8	^d <i>P</i> < 0.0001	NS	NS
IL-8 or CXCL8	50.2 ± 6.8	79.2 ± 18.0	66.9 ± 13.2	73.3 ± 9.1	^d <i>P</i> < 0.0001	NS	NS
IP-10 or CXCL10	1890.0 ± 52.7	2309.0 ± 545.1	2224.0 ± 578.5	2710.0 ± 220.1	^a <i>P</i> < 0.05	NS	^a <i>P</i> < 0.05
Eotaxin or CCL11	255.4 ± 50.4	319.8 ± 65.5	277.2 ± 51.8	328.6 ± 50.7	^b <i>P</i> < 0.01	NS	NS
Clinical psychiatric scale							
HDRS	N/A	19.4 ± 4.7	9.1 ± 4.72	6.0 ± 2.4	N/A	^d <i>P</i> < 0.0001	^d <i>P</i> < 0.0001

Values are presented as mean ± standard deviation. To compare differences between means, the homogeneity of variance test was employed in all cases, followed by one-way analysis of variance with Bonferroni's *post hoc* test when the variances were equal and Dunnett T3 test when the variances were not equal. Statistical significance was attributed when

^a*P* < 0.05;

^b*P* < 0.01 and

^d*P* < 0.0001. N/A: Not applicable; NS: Not significant. HDRS: Hamilton depression rating scale; IL-8: Interleukin-8; IP-10: Interferon gamma-induced protein 10; MCP-1: Monocyte chemoattractant protein-1; MDD: Major depressive disorder; MIP: Macrophage inflammatory protein.

MCP-1

MCP-1 is produced constitutively after induction by oxidative stress, cytokines, or growth factors and secreted by several types of cells, including monocytes, smooth muscle cells, and endothelial cells^[20]. We observed significant differences in serum MCP-1 levels between HVs and patients (HV *vs* 0 wk, 4 wk, and 8 wk) (*F* = 34.03, *df* = 80.3, *P* < 0.0001). Before beginning pharmacological treatment (0 wk), patients showed significantly higher MCP-1 levels compared with HVs (*P* < 0.0001). Notably, MCP-1 declined in patients after 4 wk of fluoxetine administration (0 wk *vs* 4 wk, *P* < 0.026) but increased at 8 wk to similar levels as in 0 wk.

MIP-1α

Normally, MIP-1α is expressed by stromal and hematopoietic stem cells and participates in cell adhesion, migration, and chemotaxis of monocytes, lymphocytes, dendritic cells, eosinophils, and natural killer (NK) cells. It is also involved in the inflammatory process, inhibits stem cell proliferation, and is a potent osteoclast activator^[21]. This protein recruits and stimulates mononuclear phagocytes in the CNS, microglia, and astrocytes, which are sources of this chemokine^[22]. Serum MIP-1α levels were higher at all time points in patients compared with HVs (*F* = 10.01, *df* = 80.3, *P* < 0.0001), but not between the 8 wk clinical follow-up (4 and 8 wk) and the beginning of

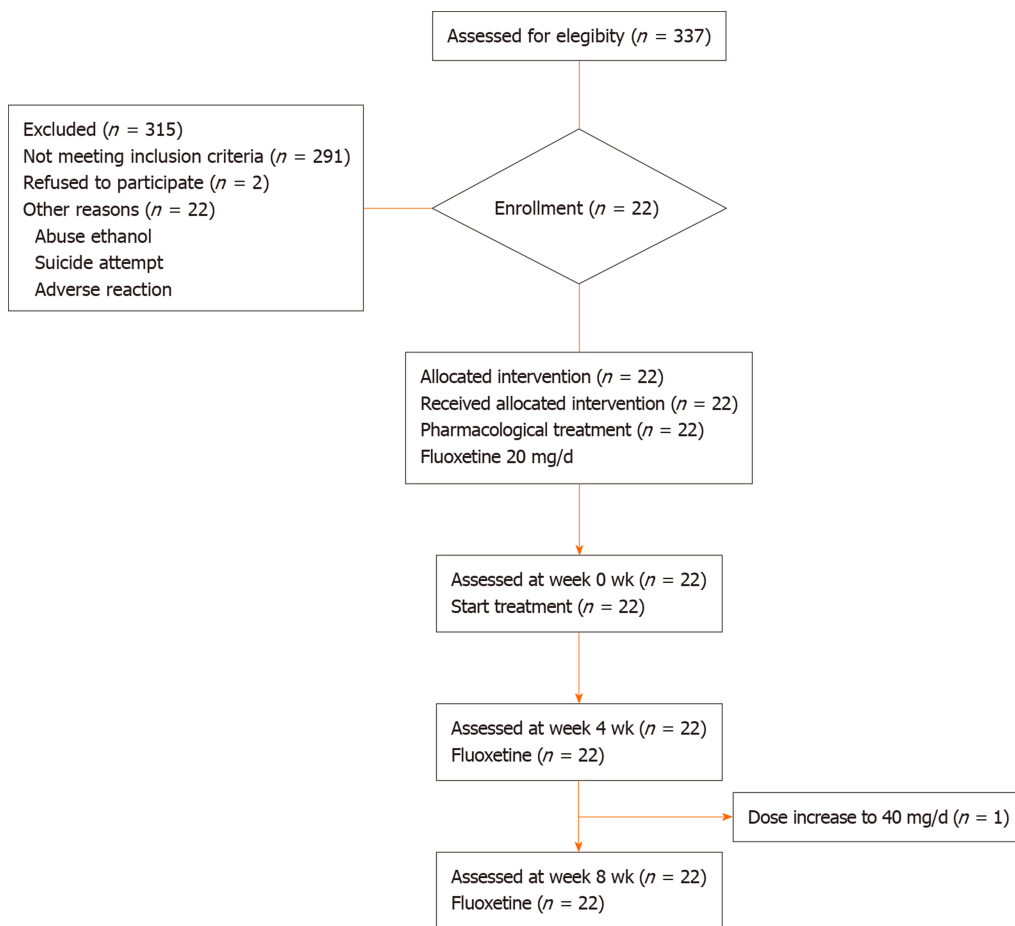


Figure 1 Flow diagram of 8-wk fluoxetine treatment for patients with major depressive disorder.

the pharmacological treatment (0 wk).

MIP-1β

MIP-1β has chemoattractive properties toward several cell types including immature dendritic cells, macrophages, monocytes, and NK cells. In addition, it induces calcium mobilization in NK cells, monocytes, leukocytes, vascular smooth muscle cells, and progenitor B cells^[23]. We observed significantly higher levels of MIP-1β in patients *vs* HVs ($F = 23.55, df = 80.3, P < 0.0001$) but no differences throughout the clinical follow-up (0, 4, and 8 wk).

IL-8

IL-8 is a chemoattractant for neutrophils and lymphocytes in inflammatory processes. We noted significant differences in serum IL-8 levels between HVs and patients during the clinical follow-up ($F = 12.74, df = 80.3; P < 0.0001$). Patients experienced a significant decrease in IL-8 from 0 wk to 4 wk ($P < 0.01$), which increased at 8 wk to similar levels as those at 0 wk.

IP-10

IP-10 is a T helper cell 1-related chemokine identified as an early-response gene induced by interferon (IFN)-γ in U937 monocytes^[24]. The IP-10 and IFN-γ levels detected in these same patients^[25] showed a correlation ($r = 0.6147, P < 0.0001$), while IP-10 levels were higher in patients (0, 4, and 8 wk) *vs* HVs ($F = 12.74, df = 80.3, P < 0.0001$). However, IP-10 levels significantly increased in patients only at 8 *vs* 0 wk ($P < 0.01$).

Eotaxin

Eotaxin is the most potent and selective factor that modulates the function of eosinophils and mediates the infiltration of eosinophils into the airway^[26]. Eotaxin is secreted primarily from bronchial epithelial cells, eosinophils, and endothelial cells. In our patients, serum eotaxin levels were higher than HVs at 0, 4, and 8 wk ($F = 8.00, df$

= 80.3, $P < 0.0001$). Serum eotaxin levels did not vary in patients throughout the clinical follow-up *vs* 0 wk.

DISCUSSION

Disturbances in serum chemokine levels are associated with the onset of major depression^[9,12-14,27,28]. These inflammatory molecules affect cell-cell interactions, neuromodulation, and synaptic transmission, all of which are altered in MDD patients^[13]. Although, a relationship between serum and cerebrospinal fluid levels of chemokines has not been demonstrated, the expression of some chemokines, chemokine ligands, and receptors in developing and mature CNS has been described under both physiological and inflammatory conditions. Astrocytes, oligodendrocytes, and microglia, as well as neuronal cells, constitutively release several chemokines including MCP-1, MIP-1 α , MIP-3, secondary lymphoid-tissue chemokine, IP-10, and fractalkine^[29,30].

Chemokines play an important role in the regulation of neuronal development and plasticity, proliferation, migration, and neural progenitor cell differentiation. For example, fractalkine regulates microglial synaptic pruning of mature neurons, modulates several neurotransmitters, and regulates the activation state of microglia^[29,30]. Therefore, these molecules influence the development and plasticity of the CNS. Exogenous application of fractalkine enhances *in vivo* neurogenesis in aged rats by modulating the microglia phenotype. Other chemokines such as MCP-1, CCL21, and monokine induced by IFN- γ (MIG), promote neuronal differentiation, whereas MCP-1, growth-regulated oncogene- α , and MIG favor oligodendrocyte differentiation. Also, chemokines present a unique class of neurotransmitters and neuromodulators that regulate cell survival and synaptic transmission. Fractalkine, which co-localize with serotonin in neurons of the dorsal raphe nucleus, may indirectly inhibit serotonin neurotransmission by upregulating the sensitivity of serotonin dorsal raphe nucleus neurons to gamma-aminobutyric acid inputs. Furthermore, the results from electrophysiological studies suggest that MCP-1, regulated upon activation, normal T cell expressed and presumably secreted, macrophage-derived chemokine, MCP-5, IL-8, and fractalkine chemokines can modulate electrical activity in the cortical, cerebral, hippocampal, and hypothalamic neurons^[29,30]. Given the number of functions in which chemokines and their receptors are involved in the CNS, they could become novel diagnostic markers or therapeutic targets for MDD, although a more significant number of studies is required.

In this work we measured serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1 α , and MIP-1 β levels in adolescents with MDD throughout 8 wk of clinical follow-up. Although other groups have reported an association between peripheral chemokine levels and the severity of depressive symptoms, there are discrepancies in their results. Furthermore, our study is the first to report the chemokine profiles in adolescents with MDD.

MCP-1

Levels of MCP-1 were high in adolescents with MDD without treatment *vs* HVs, consistent with a meta-analysis^[14]. Longitudinal studies, such as those by Sutcgil *et al*^[31], have reported similar values for MCP-1 in HVs. Their results showed MCP-1 levels of 84.54 ± 12.54 pg/mL in HVs with a mean age of 34 treated with sertraline (another SSRI) for 8 wk, after which MCP-1 levels fell by over 50%^[31]. In our clinical sample, posttreatment MCP-1 levels reached pretreatment values. Piletz *et al*^[32] reported similar findings to ours, recording high levels of MCP-1 in MDD patients (205 ± 19 pg/mL) before treatment compared with HVs (132 ± 23 pg/mL). Their patients (mean age 39) were treated with venlafaxine, a dual antidepressant, for 8 wk after which MCP-1 levels remained constant^[32].

Other groups, as Simon *et al*^[17], reported high levels of MCP-1 in MDD patients before treatment. However, their results, in subjects with a mean age of 42, had a wide SD for HVs (56.66 ± 106.19 pg/mL) and MDD patients (191.00 ± 381.69 pg/mL)^[17]. Moreover, four reports failed to detect changes in MCP-1 between patients and HVs^[33-36]. All of these studies generated results from patients and controls aged over 40 and were included in the meta-analysis by Eyre *et al*^[14]. Lehto *et al*^[13] observed lower MCP-1 levels (27.19 pg/mL) in MDD patients *vs* HVs (40.79 pg/mL); these data were obtained in 61 MDD patients with a mean age of 54.

An *in vitro* study reported that the severity of depressive symptoms is significant and positively associated with the overexpression of MCP-1 and IL-8 in

lipopolysaccharide (LPS)-stimulated human blood monocytes^[37], which partially explains the MCP-1 levels in our patients. Our data and those of Piletz *et al.*^[32] suggest that the administration of dual or selective antidepressants is insufficient to reduce MCP-1 levels in MDD patients after 8 wk, although Arreola *et al.*^[38] had contradictory findings. The significant decrease in MCP-1 in our patients after 4 wk with fluoxetine treatment suggests a partial effect of SSRIs on circulatory levels of this chemokine secreted by macrophages, which constitutively express serotonin transporter^[38]. High levels of MCP-1 have been suggested to be early-stage indicators of endothelial damage and have been detected in coronary artery disease-associated chronic renal failure^[32].

MIP-1 α

Levels of MIP-1 α were high in untreated adolescents with MDD compared with HVs and remained unaltered after 8 wk of fluoxetine treatment. No other longitudinal studies exist on this chemokine. Other groups have compared serum MIP-1 α levels between adult patients and HVs, similar to Simon *et al.*^[17]. However, the values had a wide SD for HVs (60.33 ± 95.91 pg/mL) and MDD patients (463.8 ± 706.88 pg/mL) while Merendino *et al.*^[22] only detected MIP-1 α in two of nine patients. Therefore, more studies on this chemokine in mood disorders are needed.

MIP-1 β

Although MIP-1 β has a similar response to MIP-1 α , Lehto *et al.*^[13] reported significant lower levels of MIP-1 β (45.41 ± 95.91 pg/mL) in 61 MDD patients with a mean age of 53 regarding HV levels (76.31 ± 9.84 pg/mL). Given the scarce information on this inflammatory protein, additional studies are necessary.

IL-8

IL-8 was elevated in adolescents with MDD without treatment compared with HVs, remaining at similar values despite fluoxetine treatment for 8 wk. A 2-year study including 1600 geriatric MDD patients in the Netherlands and Australia^[16,39] reported that serum IL-8 levels correlate with depressive symptoms. No subsequent longitudinal studies have been performed. Other studies have reported high circulatory levels of IL-8 in patients with MDD^[17,40].

In contrast, the meta-analysis by Eyre *et al.*^[14], which included seven studies from 1998 to 2012, assessed 560 MDD patients and concluded that there was no significant difference in serum levels of IL-8 between MDD patients and HVs ($P < 0.228$). An *in vitro* study by Suarez *et al.*^[37] reported that the severity of depressive symptoms was significant and positively associated with the overexpression of MCP-1 and IL-8 in LPS-stimulated human blood monocytes, which in part explains the IL-8 levels in our patients. IL-8 has been linked to low cognitive performance, suggesting that it has several effects on the CNS^[39]. Notably, IL-8 crosses the blood-brain barrier in infectious processes^[41].

IP-10

Our patients had significantly higher and constant levels of IP-10 than HVs during the first 4 wk of fluoxetine treatment; however, IP-10 rose significantly *vs* pretreatment levels by 8 wk and thus was the only molecule with this pattern. In contrast, Wong *et al.*^[42] reported differences in plasma levels of IP-10 in HVs (67.61 ± 1.16 pg/mL) and MDD patients (95.50 ± 1.16 pg/mL) before pharmacological treatment, whereas MDD patients experienced a decrease in IP-10 at 8 wk after beginning treatment with antidepressants (desipramine or fluoxetine). Further studies will be required to determine the behavior of this molecule in MDD patients.

In an *in vitro* study, Tsai *et al.*^[24] demonstrated that fluoxetine inhibits the secretion of IP-10 in TPH-1 cells (a cell line derived from human macrophages) that have been stimulated with LPS, in a process that is dependent on the mitogen-activated protein kinase-38 pathway. In contrast, after 8 wk on fluoxetine, IP-10 increased in our adolescents with MDD. These results are notable due to high levels of IP-10, an angiostatic factor with antifibrotic properties^[9].

Eotaxin

In a comparison between patients and HVs, we observed a significant elevation in serum eotaxin levels, which remained high throughout the clinical follow-up. There are no other longitudinal reports on this chemokine; still, there are three transversal studies showing that MDD patients had significantly higher circulatory levels of eotaxin than HVs before pharmacological treatment^[17,34,43].

It has been reported that plasma eotaxin levels are related with reduced neurogenesis in aged mice and that eotaxin levels rise in blood and cerebrospinal fluid of healthy aging humans^[44]. Notably, in our study, eotaxin rose significantly in adolescents with MDD despite treatment with fluoxetine. As in other cases, there are few studies on eotaxin in mood disorders. Based on its effects in the CNS, eotaxin inhibits IL-4 activity^[45] and IL-4 is critical in higher functions of the normal brain, such as memory and learning^[46], cognitive functions that are affected in MDD.

In this study, we observed that chemokines eotaxin, IL-8, IP-10, MCP-1, MIP-1 α and MIP-1 β were increased in comparison with HVs, and despite treatment with fluoxetine, they remained consistently high in the patient group. Although there were variations in serum chemokine levels throughout the 8 wk clinical follow-up, all adolescents with MDD experienced a significant decrease in clinical-psychiatric parameters after consuming fluoxetine, similar to the two other longitudinal studies^[31,32]. This knowledge confirms the approach that clinical-psychiatric scales only focus on the behavioral parameters and further work is necessary to identify molecular parameters of clinical utility for psychiatrists in mood disorders.

Limitation of this study

This study had some limitations. The patient number was small, although the numbers of HVs and patients were sufficient for statistical analysis. In all cases, the discrepancies between our values and those reported by other groups can be explained by differences in the sample source such as serum or plasma, detection techniques, age of the participants, and confounding factor, such as tobacco and alcohol consumption, and body mass index. Further studies will be required to validate our findings.

In conclusion, our results showed a significant elevation in serum chemokine level in adolescents with MDD despite treatment with fluoxetine and improvement in HDRS score. This prompted us to consider the multidisciplinary management of MDD patients since high levels of MCP-1 and IP-10 are associated with endothelial damage and coronary risk. The elevation in eotaxin, IP-10, and IL-8 might explain certain features of depressed patients such as impaired cognition, memory, and learning. Further studies are necessary to examine these findings and determine their implications for future therapeutic approaches in MDD patients.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) affects 350 million people, approximately 6% of whom are adolescents; however, research on this age group is limited. The depressive symptomatology in adolescents can be confused with other psychiatric disorders, in turn affecting the proper diagnosis and normal development of patients. MDD in adolescents is associated with several negative outcomes including other psychiatric disorders later in life, educational impairment, self-injury, and suicide.

Research motivation

The immune system reaches maturity at about 16 years of age and upon the central nervous system second neural pruning. This makes adolescent patients with MDD have molecular characteristics that initially differ from adults and the elderly. These particularities have not been efficiently explored.

Research objectives

This study determined the differences in circulatory levels of eotaxin, interleukin (IL)-8, interferon gamma-induced protein (IP)-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1 α and MIP-1 β in HVs and adolescents with MDD, and assessed the changes induced by antidepressants consumed during 8 wk of clinical follow-up, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors, like fluoxetine.

Research methods

We measured serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1 α , and MIP-1 β in adolescents with MDD and performed a clinical psychiatric evaluation using the Hamilton depression rating scale (HDRS). Eighteen HVs and twenty-two adolescents with MDD were monitored throughout 8 wk of clinical follow-up.

Research results

All evaluated chemokines decreased at 4 wk, but only MCP-1 and IL-8 differed significantly ($P < 0.05$) between 0 and 4 wk. In adolescents with MDD, all chemokines rose to their initial concentrations by 8 wk (*vs* 0 wk), but only IP-10 did so significantly ($P < 0.05$). All patients experienced a significant decrease in HDRS scores at 4 wk ($P < 0.0001$) and 8 wk ($P < 0.0001$) compared with 0 wk. Despite the consumption of fluoxetine, adolescents with MDD had significantly higher chemokines levels, even after considering the improvement in the HDRS score.

Research conclusions

Our results showed a significant elevation in serum chemokine levels in adolescents with MDD despite treatment with fluoxetine and an improvement in HDRS scores. This prompted us to consider the multidisciplinary management of MDD patients since high levels of MCP-1 and IP-10 are associated with coronary risk. The elevation detected in eotaxin, IP-10, and IL-8 serum levels might explain certain features of depressed patients such as impaired cognition, memory, and learning.

Research perspectives

Given the number of functions in which chemokines and their receptors are involved in the central nervous system, they could become novel diagnostic markers or therapeutic targets for MDD patients. However, a more significant number of studies are required, particularly in the adolescent population.

ACKNOWLEDGEMENTS

We appreciate the support of Juárez-Cruz E, Ortega EF, López-Bello G, and Hernandez-Ferreira E.

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