

## BRIEF COMMUNICATION

# Plasma IL-17A levels in patients with late-life depression

Smita Saraykar,<sup>1</sup> Bo Cao,<sup>1</sup> Lucelia S. Barroso,<sup>2</sup> Kelly S. Pereira,<sup>3</sup> Laiss Bertola,<sup>2</sup> Mariana Nicolau,<sup>2</sup> Jessica D. Ferreira,<sup>2</sup> Natalia S. Dias,<sup>2</sup> Erica L. Vieira,<sup>4</sup> Antonio L. Teixeira,<sup>1,4</sup> Ana Paula M. Silva,<sup>2</sup> Breno S. Diniz<sup>1,2</sup>

<sup>1</sup>Department of Psychiatry and Behavioral Sciences, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, TX, USA. <sup>2</sup>Programa de Pós-Graduação em Medicina Molecular, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. <sup>3</sup>Psychiatry Department, Instituto de Previdência dos Servidores do Estado de Minas Gerais (IPSEMG), Belo Horizonte, MG, Brazil. <sup>4</sup>Divisão de Neurociências, Laboratório Interdisciplinar de Investigação Médica, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.

**Objective:** A consistent body of research has confirmed that patients with major depressive disorder (MDD) have increased concentrations of pro-inflammatory cytokines, including IL-6, TNF- $\alpha$ , IL-1 $\beta$ , the soluble IL-2 receptor, and C-reactive protein, compared to controls; however, there is limited information on IL-17A in MDD. Moreover, information about IL-17A in older populations, i.e., patients with late-life depression (LLD), is conspicuously missing from the literature. The purpose of this study was to investigate the role of IL-17A in LLD.

**Methods:** A convenience sample of 129 individuals, 74 with LLD and 55 non-depressed controls, were enrolled in this study. The Mann-Whitney *U* test was used to compare plasma IL-17A levels between LLD and controls subjects, and Spearman's rank order correlation was used to investigate correlation of these levels with clinical, neuropsychological, and cognitive assessments.

**Results:** Plasma IL-17A levels were not statistically different between LLD patients and controls ( $p = 0.94$ ). Among all subjects (LLD + control), plasma IL-17A did not correlate significantly with depressive symptoms ( $\rho = -0.009$ ,  $p = 0.92$ ) but a significant correlation was observed with cognitive assessments ( $\rho = 0.22$ ,  $p = 0.01$ ).

**Conclusion:** Our findings do not support an association between plasma IL-17A levels and LLD. Nevertheless, IL-17A may be associated with cognitive impairment in LLD patients. If this finding is confirmed in future longitudinal studies, modulation of the T-helper 17 cell (T<sub>H</sub>17) immune response may be a treatment target for cognitive impairment in this population.

**Keywords:** Depression; cytokines; cognitive impairment; immunology

## Introduction

A consistent body of research has confirmed the bidirectional relationship between major depressive disorder (MDD) and systemic inflammation.<sup>1</sup> Patients with MDD have been shown to have increased concentrations of pro-inflammatory cytokines, including IL-6, TNF- $\alpha$ , IL-1 $\beta$ , the soluble IL-2 receptor, and C-reactive protein (CRP), compared to controls,<sup>2,3</sup> while pro-inflammatory molecules such as interferon-alpha (IFN- $\alpha$ ) may induce depressive symptoms.<sup>4</sup> Moreover, anti-inflammatory agents such as cyclooxygenase-2 (COX-2) inhibitors and *N*-acetyl-cysteine attenuate depressive symptoms.<sup>5</sup> While the link between these pro-inflammatory markers and depression is reasonably established, information on the role of IL-17A in MDD is still limited.

IL-17A is a cytokine that has been associated with chronic inflammatory conditions. It is secreted by T-helper

17 (T<sub>H</sub>17) lymphocytes and plays a key role in immune activation and in the pathogenesis of several autoimmune diseases, such as inflammatory bowel disease,<sup>6</sup> psoriasis,<sup>7</sup> and multiple sclerosis.<sup>8</sup> The high rates of comorbid depression with these syndromes may suggest common pathophysiological links. Studies in animal models have demonstrated that increased levels of IL-17A are associated with depression.<sup>9,10</sup> Human studies also reported significant elevations of IL-17A in the blood of patients with rheumatoid arthritis and anxiety when compared to those without anxiety. Additionally, plasma IL-17A levels correlated positively with severity of anxiety even after adjustment for DAS-28 and pain.<sup>11</sup> Escitalopram and sertraline are known to decrease plasma IL-17A levels in patients with depression.<sup>12</sup>

Despite growing evidence of a role of IL-17A in MDD, studies of older populations – i.e., patients with late-life depression (LLD) – are conspicuously missing from the literature. LLD is a significant public health concern, and given the relevance of immune-inflammatory dysregulation to its pathophysiology,<sup>13</sup> we designed the present study to compare IL-17A levels between LLD patients and non-depressed controls and investigate its correlation with clinical, neuropsychological, and cognitive assessments.

Correspondence: Smita Saraykar, MD, MPH, University of Texas Health Science Center at Houston, 7000 Fannin, Ste 600, Houston, TX 77030.

E-mail: smitasaraykar@yahoo.com

Submitted Apr 11 2017, accepted Jun 05 2017.

## Methods

### Sample recruitment and assessment

The study was approved by the ethics committee of Universidade Federal de Minas Gerias, Belo Horizonte, MG, Brazil. A convenience sample of 129 individuals, 74 with LLD and 55 non-depressed controls, were enrolled in this study. The LLD group was recruited from the outpatient psychogeriatric clinic of the university after referral for depressive symptoms. The criteria for inclusion in the control group included no past history of MDD, bipolar disorder, schizophrenia, or other major psychiatric disorders; and no evidence of major neurocognitive impairment. The control group was also evaluated by the same research team as part of an ongoing study about health and cognitive aging.

All participants underwent a comprehensive clinical, psychiatric, and cognitive assessment. The psychiatric assessment included the following instruments: Mini Neuropsychiatric Interview (MINI);<sup>14</sup> Hamilton Depression Rating Scale-21 items (HDRS-21);<sup>15</sup> and Generalized Anxiety Disorder Assessment-7 (GAD-7). Diagnosis of major depression and other psychiatric comorbidities was based on DSM-5 criteria. We also administered the Dementia Rating Scale (DRS)<sup>16</sup> for neurocognitive assessment and to exclude potential dementia cases in this population.

### Laboratory analysis

After psychiatric assessment, blood samples were collected by antecubital venipuncture. The plasma was separated by centrifugation and plasma aliquots were stored at -80°C until experimentation.

Plasma IL-17A levels were measured by a LUMINEX multiplex assay (Merck Millipore Corporation, Germany) in accordance with the manufacturer's instructions. All samples were analyzed in duplicate, and the laboratory analysis was done in a single run on the same day. A standard curve was created based on the following standard concentrations: blank, 3.2 pg/mL, 16 pg/mL, 80 pg/mL, 400 pg/mL, and 2,000 pg/mL. The analytical sensitivity of the assay is 0.7 pg/mL. The intra- and inter-assay coefficients of variation were 2.2% and 7.9%, respectively.

### Statistical analysis

Levels of IL-17A and clinical variables did not follow a normal distribution even after attempts at data transformation. Thus, we used the nonparametric Mann-Whitney *U* test to investigate differences in IL-17A levels. For clinical and neurocognitive variables, we used the *t* test and chi-square test. We also calculated Spearman's rank-order correlations for the entire sample, i.e., LLD + control (n=121), LLD patients (n=74), and LLD patients with no cognitive impairment (LLD + NC) (n=47) to investigate whether IL-17A levels correlated with clinical, neuropsychological, and cognitive assessments.

## Results

The main findings of this study are shown in Table 1. We found no statistically significant differences in plasma IL-17A levels ( $p = 0.94$ ), mean age ( $p = 0.27$ ), gender distribution ( $p = 0.52$ ), or body mass index (BMI) ( $p = 0.56$ ) between LLD patients and controls.

**Table 1** Comparison between patients with late-life depression (LLD) and controls

	LLD (n=74)	Control (n=55)	Statistics	df	p-value
IL-17A, mean rank	60.80	61.32			0.94*
Age	72.96 (8.09)	71.36 (7.70)	-1.09 <sup>†</sup>	119	0.28
BMI	26.64 (6.38)	27.33 (4.80)	0.57 <sup>†</sup>	86	0.56
Male-to-female ratio	4/43	9/65	0.40 <sup>‡</sup>	1	0.53
Number of medical comorbidities	3.29 (2.09)	2.72 (1.51)	-1.72 <sup>†</sup>	115.7	0.09
Medical comorbidities, n (%)					
Hypertension	51 (60.00)	34 (40.17)	0.00 <sup>‡</sup>	1	0.95
Diabetes mellitus	29 (74.36)	10 (25.64)	4.89 <sup>‡</sup>	1	0.02
Dyslipidemia	35 (64.81)	19 (35.19)	0.90 <sup>‡</sup>	1	0.34
Myocardial infarction	4 (100)	0 (0)	2.70 <sup>‡</sup>	1	0.10
Cerebrovascular accident	2 (100)	0 (0)	1.33 <sup>‡</sup>	1	0.25
HDRS-21	19.5 (6.5)	1.7 (2.5)	-21.32 <sup>†</sup>	101.52	< 0.01
DRS, total	118.9 (13.8)	131.2 (8.3)	6.07 <sup>†</sup>	118.75	< 0.01
DRS, attention	34.2 (2.7)	35.4 (1.2)	3.62 <sup>†</sup>	111.1	< 0.01
DRS, initiative and perseveration	31.3 (4.5)	34.8 (2.6)	5.39 <sup>†</sup>	118.4	< 0.01
DRS, construction	5.0 (1.3)	5.7 (0.6)	3.75 <sup>†</sup>	112.8	< 0.01
DRS, conceptualization	28.2 (6.7)	32.7 (4.9)	4.24 <sup>†</sup>	116.8	< 0.01
DRS, memory	19.0 (4.3)	22.3 (1.9)	5.86 <sup>†</sup>	108.4	< 0.01

Data presented as mean (standard deviation), unless otherwise specified.

BMI = body mass index; df = degrees of freedom; DRS = Dementia Rating Scale; HDRS = Hamilton Depression Rating Scale;

IL-17A = interleukin 17A; LLD = late-life depression.

\* *U* test.

<sup>†</sup> *t* test.

<sup>‡</sup> Chi-square test.

Among all subjects (LLD + control) ( $n=121$ ), plasma IL-17A levels did not correlate significantly with age ( $\rho = 0.08$ ,  $p = 0.36$ ), BMI ( $\rho = -0.08$ ,  $p = 0.41$ ), number of medical comorbidities ( $\rho = -0.05$ ,  $p = 0.59$ ), depression (HRDS-21 scores:  $\rho = -0.009$ ,  $p = 0.92$ ), age at first depressive episode ( $\rho = 0.02$ ,  $p = 0.59$ ), DRS Attention ( $\rho = 0.09$ ,  $p = 0.30$ ), DRS Conceptualization ( $\rho = 0.15$ ,  $p = 0.10$ ), or DRS Memory ( $\rho = 0.06$ ,  $p = 0.50$ ). However, significant correlations were seen with total DRS score ( $\rho = 0.22$ ,  $p = 0.01$ ), DRS Initiative and Perseveration ( $\rho = 0.23$ ,  $p = 0.01$ ), and DRS Construction ( $\rho = 0.19$ ,  $p = 0.03$ ).

Among LLD patients ( $n=74$ ), plasma IL-17A levels showed significant correlations with BMI ( $\rho = -0.29$ ,  $p = 0.04$ ) and total DRS score ( $\rho = 0.29$ ,  $p = 0.01$ ), but not with age ( $\rho = -0.09$ ,  $p = 0.45$ ), total number of comorbidities ( $\rho = -0.65$ ,  $p = 0.59$ ), depression ( $\rho = -0.06$ ,  $p = 0.62$ ), age at first depressive episode ( $\rho = 0.09$ ,  $p = 0.44$ ), DRS Attention ( $\rho = 0.02$ ,  $p = 0.86$ ), DRS Initiative and Perseveration ( $\rho = 0.29$ ,  $p = 0.01$ ), DRS Construction ( $\rho = 0.16$ ,  $p = 0.17$ ), DRS Conceptualization ( $\rho = 0.17$ ,  $p = 0.14$ ), or DRS Memory ( $\rho = 0.05$ ,  $p = 0.68$ ).

Among LLD patients with no cognitive impairment (LLD + NC) ( $n=47$ ), plasma IL-17A correlated significantly with age ( $\rho = 0.37$ ,  $p = 0.01$ ) but not with any other variable of interest, including depression ( $\rho = 0.12$ ,  $p = 0.43$ ), total DRS score ( $\rho = 0.15$ ,  $p = 0.30$ ), DRS Attention ( $\rho = 0.22$ ,  $p = 0.13$ ), DRS Initiative and Perseveration ( $\rho = 0.15$ ,  $p = 0.30$ ), DRS Construction ( $\rho = 0.24$ ,  $p = 0.1$ ), DRS Conceptualization ( $\rho = 0.07$ ,  $p = 0.61$ ), DRS Memory ( $\rho = 0.07$ ,  $p = 0.64$ ).

## Discussion

To the best of our knowledge, this was the first study to evaluate circulating levels of IL-17A in LLD. We did not find a statistically significant difference in plasma IL-17A levels between patients with LLD and non-depressed elderly controls. Previous studies that evaluated the relationship between MDD and IL-17A expression have shown contradictory results. Chen et al.<sup>17</sup> investigated the mechanism of autoimmunity in MDD patients and found that  $T_H17$  cells played a potential role in the autoimmune process involved in MDD. On the other hand, Kim et al.<sup>18</sup> did not find evidence to support the involvement of IL-17A in MDD. Both studies evaluated young adults with MDD. Our results are in line with the latter study, as we did not find an association between plasma IL-17A levels and MDD in older adults. Interestingly, we found a significant correlation between plasma IL-17A and DRS scores (total, initiative and perseveration, and construction domains). This suggests that IL-17A may be relevant to the emergence of cognitive impairment in this group of patients. This is in line with recent studies from our group, which demonstrated that cognitive impairment in LLD is associated with significant abnormalities in immunoinflammatory pathways. Patients with LLD and mild cognitive impairment were found to have differential expression of 24 proteins related to regulation of immunoinflammatory activity.<sup>19</sup>

Multiple lines of evidence have shown that inflammatory abnormalities are implicated in the pathophysiology of major depression in older adults.<sup>13,20,21</sup> These studies evaluated cytokines related to  $T_H1$  and  $T_H2$  cells, but not to  $T_H17$  lymphocytes. To bridge this knowledge gap, the focus of this study was to evaluate the role of  $T_H17$  response in LLD. Our preliminary results may indicate that the abnormal inflammatory response observed in LLD is due to dysregulation of  $T_H1$  and  $T_H2$ , but not  $T_H17$ , immune responses. We did not assess other cytokines, as there is a wealth of literature evaluating other pro-inflammatory cytokines ( $T_H1$ ,  $T_H2$ , and innate immune response) in LLD. However, very few studies have assessed the role of IL-17A in patients with MDD, and essentially none in older adults with MDD. The strength of our study lies in the fact that it is one of the first to compare IL-17A levels between LLD patients and controls and investigate the correlation of IL-17A levels with clinical and neurological variables.

Our results must be viewed in light of their limitations. This was a single-center study with a small sample, and participants were recruited from a specialized geriatric psychiatry clinic, which limits generalizability of our findings. The cross-sectional design precludes any causal inferences for the relationship between IL-17A, depressive symptoms, and cognitive dysfunction in LLD. Selection bias is yet another limiting factor. Therefore, our results should be replicated in independent, preferably longitudinal studies with large samples of patients on and off antidepressants.

In conclusion, our findings do not support the hypothesis of an association between plasma IL-17A levels and LLD. Nonetheless, IL-17A might be associated with cognitive impairment among older adults with depression. Further studies are needed to investigate the relationship between IL-17A and cognitive impairment in LLD. If this finding is confirmed in future studies, modulation of the  $T_H17$  immune response may be a treatment target for cognitive impairment in this population.

## Acknowledgements

This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grants 466623/2014-3 and 472138/2013-8 [BSD]).

## Disclosure

The authors report no conflicts of interest.

## References

- 1 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65:732-41.
- 2 Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67:446-57.
- 3 Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58:445-52.
- 4 Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, Hill J, et al. A prospective study of the incidence and open-label treatment of

- interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry*. 2002;7:942-7.
- 5 Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*. 2014;71:1381-91.
  - 6 Shen W, Durum SK. Synergy of IL-23 and Th17 cytokines: new light on inflammatory bowel disease. *Neurochem Res*. 2010;35:940-6.
  - 7 Maeda S, Hayami Y, Naniwa T, Ueda R. The Th17/IL-23 axis and natural immunity in psoriatic arthritis. *Int J Rheumatol*. 2012;2012:539683.
  - 8 Hong J, Hutton GJ. Regulatory effects of interferon-beta on osteopontin and interleukin-17 expression in multiple sclerosis. *J Interferon Cytokine Res*. 2010;30:751-7.
  - 9 Kim SJ, Lee H, Lee G, Oh SJ, Shin MK, Shim I, et al. CD4+ CD25+ regulatory T cell depletion modulates anxiety and depression-like behaviors in mice. *PLoS One*. 2012;7:e42054.
  - 10 Tallerova AV, Kovalenko LP, Durnev AD, Seredenin SB. [Effect of antiasthenic drug ladasten on the level of cytokines and behavior in experimental model of anxious depression in C57BL/6 male mice]. *Eksp Klin Farmakol*. 2011;74:3-5.
  - 11 Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *Int J Rheum Dis*. 2012;15:183-7.
  - 12 Munzer A, Sack U, Mergl R, Schonherr J, Petersein C, Bartsch S, et al. Impact of antidepressants on cytokine production of depressed patients in vitro. *Toxins (Basel)*. 2013;5:2227-40.
  - 13 Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. *Int J Geriatr Psychiatry*. 2011;26:1109-18.
  - 14 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59:22-33; quiz 34-57.
  - 15 Miller IW, Bishop S, Norman WH, Maddever H. The modified Hamilton rating scale for depression: reliability and validity. *Psychiatry Res*. 1985;14:131-42.
  - 16 Marson DC, Dymek MP, Duke LW, Harrell LE. Subscale validity of the Mattis Dementia Rating Scale. *Arch Clin Neuropsychol*. 1997;12:269-75.
  - 17 Chen Y, Jiang T, Chen P, Ouyang J, Xu G, Zeng Z, et al. Emerging tendency towards autoimmune process in major depressive patients: a novel insight from Th17 cells. *Psychiatry Res*. 2011;188:224-30.
  - 18 Kim JW, Kim YK, Hwang JA, Yoon HK, Ko YH, Han C, et al. Plasma levels of IL-23 and IL-17 before and after antidepressant treatment in patients with major depressive disorder. *Psychiatry Investig*. 2013;10:294-9.
  - 19 Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, et al. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. *Mol Psychiatry*. 2015;20:594-601.
  - 20 Diniz BS, Lin CW, Sibille E, Tseng G, Lotrich F, Aizenstein HJ, et al. Circulating biosignatures of late-life depression (LLD): towards a comprehensive, data-driven approach to understanding LLD pathophysiology. *J Psychiatr Res*. 2016;82:1-7.
  - 21 Smagula SF, Lotrich FE, Aizenstein HJ, Diniz BS, Krystek J, Wu GF, et al. Immunological biomarkers associated with brain structure and executive function in late-life depression: exploratory pilot study. *Int J Geriatr Psychiatry*. 2017;32:692-9.