ASSOCIATION BETWEEN LYMPHOCYTES, HIPPOCAMPUS VOLUME AND DEPRESSIVE SYMPTOMS IN *DRUG – NAÏVE* FIRST EPISODE PSYCHOSIS

A. Toll (1,2,3), D. Bergé (1,2,3), K. El-Abidi (1), T. Legido (1,2), C. Fernandez-Hinchado (4), V. Pérez-Solà (1,2,3), A. Mané (1,2,3)

1. Institut de Neuropsiquiatria i Adiccions (INAD), Parc de Salut Mar, Barcelona, Spain.
2. Fundació Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.
3. Centro de Investigación Biomédica en Red, Área de Salud Mental (CIBERSAM), Spain.
4. ESM Rural, Montijo - Puebla de la Calzada, Extremadura, Spain.

INTRODUCTION

Schizophrenia is a chronic and heterogeneous metal disorder associated with a great disability [1]. Its underlying pathophysiology remains unclear being most likely multifactorial, attributable to both genetic and environmental factors. One of the most promising theories proposes that the immune system is involved in the etiology of schizophrenia, either due to immunological alterations or autoimmune mechanisms.

The relationship between the immune system and the central nervous system (CNS) is hugely complex. However, it has been proposed that increased brain pro-inflammatory status, decreased neurotrophic function, and brain increased production of neurotoxic cytokines, could play a vital role in the pathophysiology of schizophrenia [2].

Specifically, some animal studies have suggested that lymphocytes, particularly T-cells, have a protective effect in the brain [3], stimulate neurogenesis [4] and have a beneficial effect in hippocampal-dependent learning [5].

Circulating white blood cells (leucocytes), which form the peripheral immune system, are crucial in inflammatory processes but their role in brain structural change in schizophrenia has been scarcely studied.

OBJECTIVES

Determine how white blood cells are associated with some brain structures volumes in first episode psychosis (FEP) and their relationship with clinical variables at baseline and 1 year follow – up.

METHODS

Fifty *drug-naïve* FEP treated between April 2013 and July 2017 at the ETEP Program at Hospital del Mar were included. Inclusion criteria were: **1)** age 18-35 years; **2)** fulfillment of DSM-IV-TR criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or unspecified psychosis; **3)** no previous history of severe neurological medical conditions or severe traumatic brain injury; **4)** presumed IQ level > 80, and **5)** no substance abuse or dependence disorders except for cannabis and/or nicotine use. All patients underwent an assessment at baseline and at one-year follow-up, including sociodemographic and clinical variables (substance use, DUP, PANSS, GAF and CDSS). Fasting blood samples were obtained before administering any medication at baseline. Structural T1 MRI was performed at baseline and brain volumes were quantified though FreeSurfer software. SPSS program was used for statistical analyzes.

RESULTS

Lymphocytes have a positive correlation with right and left hippocampus at baseline (p = 0.049; p = 0.015). The other white blood cells lines did not have any correlation with left and right hippocampal volume. Moreover, lymphocytes have a negative correlation with depressive symptoms at baseline (p = 0.008) and 1 year follow – up (p = 0.009) and 1 year follow – up.

Table 1. Sociodemographic, clinical, biochemical and volumetric characteristics of FEP patients at baseline at 1 year follow - up.

Variable	Baseline	1 year follow - up
Age, median (M, IQR)	26 (24 - 30.25)	
Sex, n (% female)	22 (44)	
DUP, median (M, IQR)	31 (8 - 115)	
Cannabis use, n (% users)	29 (58)	
Tobacco use, median (M, IQR)	4.5 (0 - 14)	
PANSS P score (m, sd)	24.88 (6.74)	12.69 (7.03)
PANSS N score (m, sd)	16.86 (6.65)	17.18 (5.89)
PANSS GP score (m, sd)	43.68 (8.27)	31.67 (9.22)
PANSS T score (m, sd)	85.24 (15.76)	62.51 (19.39)
CDSS score (m, sd)	1.22 (2.02)	0.64 (1.11)
GAF score (m, sd)	29.7 (8.89)	61.18 (17.68)
Leukocytes (m, sd)	11.89 (7.04)	
Neutrophils (m, sd)	8.99 (6.89)	
Lymphocytes (m, sd)	1.95 (0.76)	
Monocytes (m, sd)	0.81 (0.44)	
Basophils (m, sd)	0.13 (0.13)	
Eosinophils (m, sd)	0.03 (0.02)	
Relative left hippocampus in mL (m, sd)	2.64 (0.27)	
Relative right hippocampus in mL (m, sd)	2.78 (0.31)	

*All values given as means with SD, unless otherwise indicated.

Abbreviations: N = Sample size, IQR = Interquartile range, mL = milliliters, DUP = Duration untreated psychosis, IQR = Interquartile range, n = Sample size, PANSS P = Positive and Negative Syndrome Scale positive, PANSS N = Positive and Negative Syndrome Scale negative, PANSS GP = Positive and Negative Syndrome Scale general pathology, PANSS T = Positive and Negative Syndrome Scale total, CDSS = Calgary Depression Scale for Schizophrenia, GAF = Global Assessment of Functioning

Figure 1. Correlation between lymphocytes and right and left hippocampus in FEP patients at baseline.

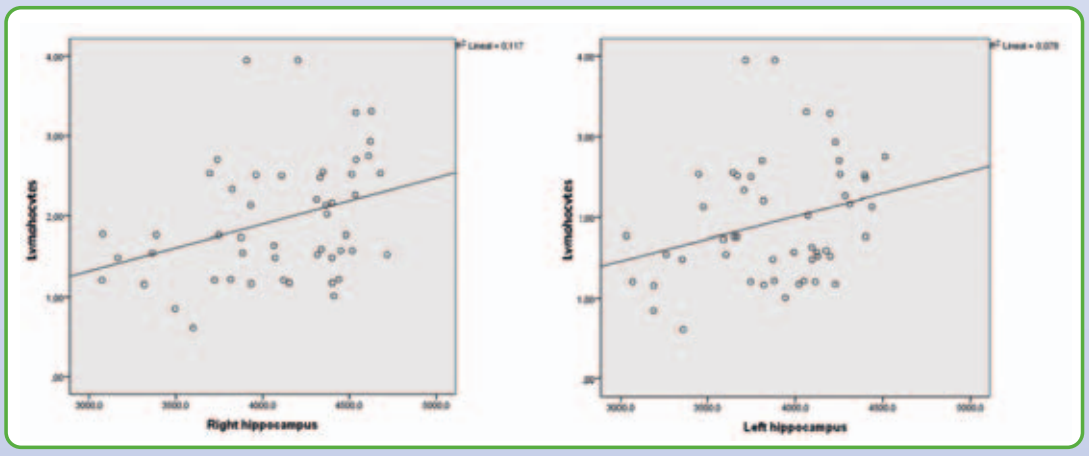
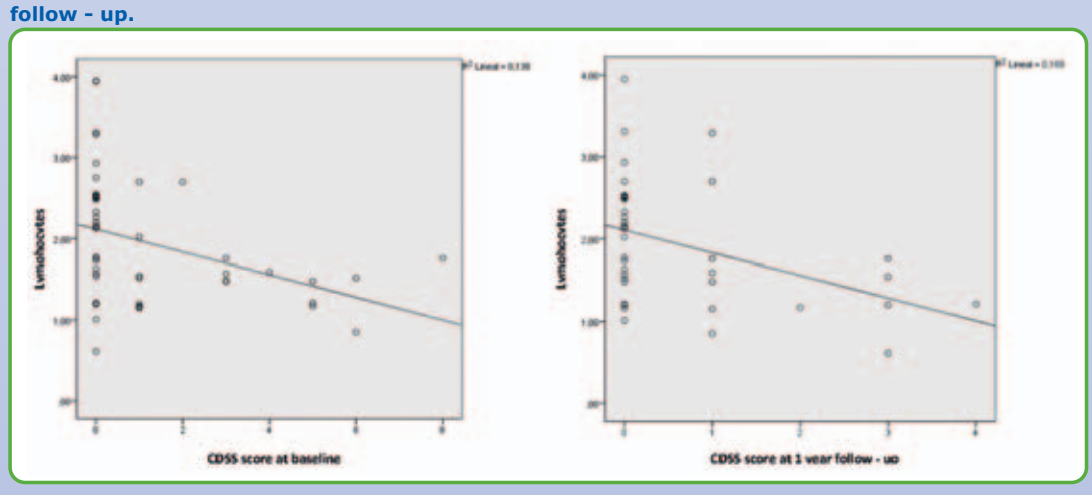


Figure 2. Correlation between lymphocytes and CDSS score in FEP patients at baseline and 1 year follow - up.



CONCLUSIONS

Lymphocytes may have a protective effect in some brain structures in FEP patients at baseline, especially those implicated in depressive symptoms.

Further, using lymphocytes as biomarker would have the advantage of being inexpensive and handy, as it can be quantified with a single blood sampling. Altogether, these results open the door to identify new therapeutic targets for neuropsychiatric related disorders through modulating adaptive immune response. Nevertheless, more research should assess whether therapies of this kind could potentially improve the course of the psychotic disorders or even stop its progression.

** The authors have no conflicts of interest to declare that are relevant to the content of this study.*

REFERENCES

1. Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. PLoS One. 2012;7(3):e31660.
2. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull. 2014 Jan;40(1):181-91.
3. Serpe CJ, Coers S, Sanders VM, Jones KJ. CD4+ T, but not CD8+ or B, lymphocytes mediate facial motoneuron survival after facial nerve transection. Brain Behav Immun. 2003 Oct;17(5):393-402.
4. Ritzel RM, Pan SJ, Verma R, Wizeman J, Crapser J, Patel AR, Lieberman R, Mohan R, McCullough LD. Early retinal inflammatory biomarkers in the middle cerebral artery occlusion model of ischemic stroke. Mol Vis. 2016 Jun 4;22:575-88.
5. Radjavi A, Smirnov I, Kipnis J. Brain antigen-reactive CD4+ T cells are sufficient to support learning behavior in mice with limited T cell repertoire. Brain Behav Immun. 2014 Jan;35:58-63.