

CORTICAL VOLUME IS INVERSELY CORRELATED WITH INTERLEUKIN-6 SERUM LEVELS IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

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Introduction: It is well established that cortical volume are decreased in patients with schizophrenia. One possible explanation is that the increased pro-inflammatory status in schizophrenia is related to volumetric decrease of gray matter. The aim of this study was to correlate interleukin 6 (IL-6) with cortical volume in patients with schizophrenia and controls.

Methods: We selected 36 patients with schizophrenia and 35 controls. Interleukin 6 (IL-6) was correlated with cortical volume in patients with schizophrenia and controls.

Results: IL-6 was negatively correlated with cortical volume ($p = 0.027$; $\rho = -0.370$) in patients, but not in controls ($p = 0.235$).

Discussion: Our results are in line with previous studies suggesting that chronic inflammatory activation in patients with schizophrenia could be one plausible mechanism that could contribute for the cortical volumetric decrease often seen in this population. However, this cross-sectional study with a small number of patients does not allow us to establish causal relations.

Keywords: *Schizophrenia; Inflammation; MRI*

INTRODUCTION

Schizophrenia may be associated with progressive enlargement of brain ventricles¹. Although not conclusive, structural deficits noted in studies include increased lateral ventricular volumes, decreased frontal lobes and thalamic volumes, grey matter loss within the anterior cingulate, superior temporal gyrus and hippocampus, and decreased overall cerebral size². The progressive volume changes in temporal and frontal lobes observed in patients with schizophrenia are striking in light of cross-sectional magnetic resonance imaging (MRI) studies showing particularly prominent volume deficits in these regions. Decline in temporal lobe tissue or gray matter was observed in patients with childhood-onset and first-episode schizophrenia³. The hippocampal volume of anyone is the result of several features; for instance, the presence and severity of comorbidities (like diabetes mellitus), as well as therapeutic measures aiming to get better fitness, can enlarge the size of the hippocampus. Besides that, the size of the hippocampus, as much as the whole brain, is associated with individual's height – the intracranial contents are scaled to the size of the cranial cavity. Many medical conditions can influence the size of the hippocampus with ageing, including vascular risk factors and cardiovascular disease, as well as other common diseases like traumatic brain injury and clinical depression. The pronounced cognitive decline observed in patients after cardiac arrest, obesity, diabetes mellitus, atrial fibrillation, hypertension, or obstructive sleep apnea can be related to hippocampal atrophy. Usually, multiple vascular risk factors are present in the

same patient and can have synergistic outcomes in the normal ageing of the brain. Nevertheless, a single risk factor can also influence cognitive function through a reduction in the size of the whole brain, and the hippocampus in particular. To exemplify, children with heart failure have a great reduction in hippocampal volume without obesity, hypertension, and other vascular comorbidities⁴.

Cytokines regulate inflammation and coordinate both innate and adaptive arms of the immune system, being important mediators of the cross-talk between the central nervous system and the immune system, which might have implications for clinical psychiatry⁵.

Examples of cytokines include interleukins (IL) and tumor necrosis factors (TNF). IL-1, IL-6 and TNF-alpha are considered pro-inflammatory, in the sense that they augment the immune response to infection and inflammation by promoting leukocyte recruitment to inflammatory sites and/or by activating inflammatory cells⁶. IL-10 is an anti-inflammatory cytokine that contributes to dampen the immune and inflammatory response⁶. Thiobarbituric acid-reactive substances is one of the well-known secondary products of lipid peroxidation and was used as an indicator of oxidative damage for several diseases⁷.

A chronic inflammatory state with increased levels of pro-inflammatory cytokines and altered levels of Th-1-like and Th-2-like cytokines may characterize schizophrenia⁸. Hypothesized signs of inflammation and monocyte activation include increased levels of pro-inflammatory cytokines, e.g. TNF- α , IL-1 and IL-6, acute phase proteins, and complement factors⁹.

Oxidative damage is a mechanism of cellular injury in a number of conditions, including cancer, inflammatory states, and neurodegeneration¹⁰. Increased neuronal oxidative stress levels produce deleterious effects on signal transduction, structural plasticity, and cellular resilience, mostly by inducing lipid peroxidation in membranes and direct damage in protein and genes¹¹. Neurons and glia are particularly vulnerable to inflammatory processes and redox status, and are dependent on the maintenance of neurotrophic activity¹². Furthermore, oxidative stress has been identified as a possible element in the neuropathological processes of schizophrenia¹³.

IL-6 has been associated with brain anatomical abnormalities in animal studies. Modeling the association between prenatal infection/inflammation and schizophrenia-related disorders in rodent models of prenatal immune activation has yielded a plethora of experimental data which strongly support the utility of these models in preclinical schizophrenia research. The poly(I:C) model in mice and rats is one of the currently available prenatal immune activation models which holds strong promise in this research area. The heuristic value of the poly(I:C) model for preclinical schizophrenia research is supported

because it successfully accounts for several aspects of schizophrenia epidemiology, pathophysiology, symptomatology and treatment¹⁴. The aim of this study was to correlate interleukin 6 (IL-6) with cortical volume in patients with schizophrenia and controls.

METHODS

Seventy-one subjects were enrolled to this study protocol, 36 patients with schizophrenia (28 males; mean age 37.17 ± 12.05 ; years of disease 15.56 ± 11.75) and 25 controls (21 males, mean age 36.97 ± 13.04). Inclusion criteria for patients and controls have been described elsewhere¹⁵. All patients received pharmacological treatment by their psychiatrist according to clinical protocols. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki and the local ethics committee approved the study protocol.

The Structured Clinical Interview for DSM-IV (SCID) Axis I and Axis II was administered to confirm diagnosis. Sociodemographic, clinical and pharmacological data were collected via a structured interview with the patient and examination of clinical records. Trained raters assessed the psychopathological status by the 18-item Brief Psychiatric Rating Scale (BPRS)¹⁶. Each subject had 5 mL blood samples collected by venipuncture without anticoagulants, and serum was obtained by centrifugation at 300 g for 5 min and kept frozen at 70 °C for up to 6 months, until the assay. Serum IL-6 was measured according to the procedures supplied by the manufacturer using highly sensitive sandwich-ELISA kits for IL-6 (Quantikine, R&D Systems, Minneapolis, USA). All samples were assayed in duplicates.

T1-weighted magnetic resonance images were acquired with a Philips Achieva 1.5 Tesla scanner (Amsterdam, the Netherlands). The cortical volumetric segmentations were performed with the Freesurfer image analysis suite v.5.1.0, (<http://surfer.nmr.mgh.harvard.edu/>), an automated software that allows the MRI measurement of cortical and intracranial volumes¹⁷. All images were processed and checked by the same researcher. Intracranial volume was regressed out from total cortex volume.

Demographic and clinical characteristics were analyzed using chi-square, Mann-Whitney or *t*-test. The correlation between cortex volume and IL-6 serum levels was obtained by Spearman-rank correlation coefficient.

RESULTS

Demographic data and comparisons between groups are shown in Table 1. IL-6 was negatively correlated with cortical volume ($p = 0.027$; $\rho = -0.370$) in patients but not in controls ($p = 0.235$).

Table 1: Characteristics of healthy controls and patients with schizophrenia.

	Healthy controls (n = 35)	Patients with schizophrenia (n = 36)	p-value
Gender (male/female)	21/14	28/8	0.11 ^b
Age ^a	36.97 (13.04)	37.17 (12.05)	0.94 ^c
Years of education ^a	10.86 (2.54)	10.42 (3.16)	0.52 ^c
Cortical volume (cm ³) ^d	475.62 (467.66-483.58)	439.60 (431.75-447.46)	< 0.001
IL-6 ^e	7.51 (1.43)	6.99 (1.99)	0.61 ^f
Intracranial volume (cm ³)	1587.86 (141.16)	1583.58 (166.27)	0.91 ^c
Correlation of cortex volume and IL-6 (pg/mL) ^g	-0.206	-0.370*	

^a Mean (standard deviation); ^b Chi-square; ^c T-test; ^d ANCOVA with estimated mean (95% confidence interval). Covariates: age, years of education, and intracranial volume; ^e Median (interquartile range); ^f Mann-Whitney test; ^g Intracranial volume was regressed out from cortical volume. Spearman correlation (rho).

* p < 0.05

DISCUSSION

In our study, we found a correlation between IL-6 and cortical volume in patients with schizophrenia. Increased pro-inflammatory tonus has been one theory for the gray matter loss in schizophrenia. Many studies highlight the importance of IL-6 as a protagonist in this inflammatory scenario, at least in acute phases⁵. There are some limitations in the present study. It is a cross-sectional study; longitudinal studies are needed to correlate inflammation to cortical volume. An important limitation of our study is that we did not correlate brain volumes and IL-6 levels with cigarette smokers, although cross-sectional brain imaging studies suggest that healthy subjects who smoke cigarettes show smaller gray matter volumes and/or densities in the prefrontal, anterior

cingulate, occipital, and temporal cortices (including parahippocampal gyrus), thalamus, substantia nigra and cerebellum as compared to non-smokers¹⁸. Our results are in line with previous studies suggesting that chronic inflammatory activation in patients with schizophrenia could be one plausible mechanism that could contribute for the cortical volumetric decrease often seen in this population. However, this cross-sectional study with a small number of patients does not allow us to establish causal relations.

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