Journal of Neuroimmunology 283 (2015) 50–57

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

The interleukin 1 alpha, interleukin 1 beta, interleukin 6 and alpha-2-macroglobulin serum levels in patients with early or late onset Alzheimer's disease, mild cognitive impairment or Parkinson's disease

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ARTICLE INFO

Article history:
Received 24 December 2014
Accepted 24 April 2015

Keywords:
Alzheimer's disease
Mild cognitive impairment (MCI)
Parkinson's disease (PD)
Interleukin 1 alpha (IL-1α)
Interleukin 1 beta (IL-1β)
Interleukin 6 (IL-6)
Alpha-2 macroglobulin (α2-macroglobulin)
Tumor necrosis factor alpha (TNFα)
Brain derived neurotrophic factor (BDNF)
Interleukin 10 (IL-10)
Heat shock protein 90 (Hsp90)
Biomarker

ABSTRACT

Alzheimer's disease (EOAD, LOAD), mild cognitive impairment (MCI), Parkinson's disease (PD) and healthy controls were included to determine the serum interleukin-1s (IL-1α, IL-1β), IL-6 and alpha-2-macroglobulin (α_2M) levels using ELISA.

IL-6 might be a significant contributor to the inflammatory response in LOAD. The MCI data indicate that IL-1s, α_2M and BDNF are somehow related, and this relationship might allow MCI patients to be more similar to the healthy controls.

A correlation analysis of multiple biomarkers in different neurodegenerative disorders might be more useful than determining the levels of a single cytokine in a single disorder.

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1. Introduction

Neuroinflammation is a process that is suggested to contribute to the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and many others (Brosseron et al., 2014). Interleukin-1-alpha (IL-1α), interleukin-1-beta (IL-1β), and interleukin-6 (IL-6), which are the most potent inflammatory cytokines, are products of activated microglia and astrocytes and are up-regulated in AD brains (McGeer and McGeer, 2001).

The IL-1 family consists of 11 cytokines (IL-1 to IL-11) that are key factors in regulating inflammatory response to infections and sterile insults (Dinarello, 2011). Primarily, IL-1α is a membrane-anchored molecule and has autocrine signaling mechanisms; however, IL-1β is a secreted molecule that acts in a paracrine manner or systemically (Weber et al., 2010).

IL-6 is a multifunctional cytokine that can induce an acute phase response, triggered during the early course of an infection. IL-6 expression was demonstrated to be induced by tumor necrosis factor alpha (TNFα) and IL-1β administrations in cell cultures (Ringheim et al., 1995; Gadient and Otten, 1997). In contrast, IL-6 was reported to have anti-inflammatory effects by inhibiting TNFα and IL-1 production and by inducing IL-10 and the IL-1 receptor antagonist (IL-1ra) (Petersen and Pedersen, 2006).

Alpha-2 macroglobulin (α_2M) is a unique molecule among the members of the alpha-macroglobulin family due to its ability to inhibit any protease, regardless of the active catalytic site or the specificity of the protease (Roberts, 1985). α_2M has the ability to bind several cytokines, including IL-1β and IL-6. However, its action on these two molecules differs as α_2M inhibits IL-1β, while IL-6 remains active after it binds to α_2M. α_2M has an important role in the immune response by

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http://dx.doi.org/10.1016/j.jneuroim.2015.04.014
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protecting IL-6 from proteolytic reactions. α_2M also binds to TNFα and prevents its activity (Rehman et al., 2013).

As recently reviewed by Brosseron et al., there are many controversial or inconclusive reports, even on the frequently studied cytokine levels such as TNFα, IL-1, and IL-6 (Brosseron et al., 2014). To gain a better understanding of neuroinflammation in neurological disorders it would be better for researchers to investigate the potential of cytokines as biomarkers with a perspective that includes a group of molecules, such as proinflammatory cytokines or inhibitory cytokines, in different types of patient groups, such as AD, PD, mild cognitive impairment (MCI) or vascular dementia. Rather than investigating the sole effect of a cytokine in a single disease, this perspective might provide an opportunity to determine a pattern of the investigated cytokines in different neurodegenerative disorders, which in turn would allow other investigators to test the patterns in different populations. Another benefit of this approach would be that although it would not minimize the interlaboratory differences in techniques, the brand of kits, or the disposables that were used, it would provide a clearer view of the cytokine profile that is investigated in a disease.

Given that, we chose IL-1α and IL-1β as the proinflammatory cytokines and IL-6 as the pro-inflammatory or anti-inflammatory cytokine that can regulate IL-1 and α_2M as potent regulators of IL-1 and IL-6. We included four patient groups with AD (early-or late-onset), PD and MCI in this study to investigate the systemic reflection of the initiation of the neuroinflammatory process in neurodegenerative disorders with different molecular backgrounds. In addition to IL-1α, IL-1β, IL-6 and α_2M, the present study included comparisons of brain derived neurotrophic factor (BDNF), TNFα, heat shock protein 90 (Hsp90), complement factor H (CFH) and IL-10 data of the same sample group that we have previously published (Gezen-Ak et al., 2013).

2. Material and methods

2.1. The patient and control groups

Three hundred and ninety-five patients suffering from dementia or PD were recruited to the study. The dementia patients were clinically diagnosed according to DSM-IV criteria at the Behavioral and Movement Disorders Unit of the Istanbul Faculty of Medicine at Istanbul University. The patients with PD who were admitted to the Movement Disorders outpatient unit at Istanbul University, Cerrahpasa Faculty of Medicine, Department of Neurology or Behavioral and Movement Disorders Unit of the Istanbul Faculty of Medicine at Istanbul University and met the UK Brain Bank criteria were prospectively enrolled in the study. The age at examination, gender, PD duration at examination, affected side and predominant symptoms at onset were gathered from the medical records. The severity of PD was assessed according to Hoehn–Yahr staging. The Parkinsonian features were scored according to the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS). For each evaluated motor item, the score of the limb with the highest value was recorded. The functional ability was assessed using the activities of daily life (ADLs) section of the UPDRS and the Schwab and England ADL scale. All of the PD patients were under dopaminergic treatment, which was calculated as the levodopa equivalent daily dose (LEDD).

Four patient groups were established according to the age and disease status, after excluding patients with inflammatory diseases, autoimmune disease, infectious or psychiatric disease, non-Alzheimer's dementia (other than MCI), chronic heart disease, patients taking antibiotics or non-steroidal anti-inflammatory drugs, or who had significant laboratory abnormalities. The patients included in the study had erythrocyte sedimentation rates within the reference values. The healthy controls were free from any neurodegenerative disorders. A neuropsychological assessment using the Mini Mental Status Examination (MMSE) was performed for the patient and control groups. The groups were as follows: early-onset Alzheimer's disease-EOAD, late-onset Alzheimer's disease-LOAD, mild cognitive impairment-MCI, Parkinson's disease-PD, healthy control individuals whom age matched to the EOAD group and healthy control individuals whom age matched to the LOAD, MCI and PD groups. The demographics of each group were given in Table 1. Peripheral venous blood samples were collected from each individual into serum tubes. The participants were treated according to the ethical principles for medical research involving human participants described in the World Medical Association's Declaration of Helsinki, and the study was approved by the Ethics Committee of Istanbul University. Signed informed consent was obtained from all of the study participants.

2.2. ELISA assay

Human Interleukin-1-alpha Platinum ELISA kit (BMS243/2 Affymetrix, San Diego, USA; standard range (SR):1.6–100 pg/mL; sensitivity: 1.1 pg/mL, sample dilution factor (SDF): 2); Human Interleukin-1-beta Platinum ELISA kit (BMS224/2, Affymetrix, San Diego, USA; SR: 3.9–250 pg/mL; sensitivity: 0.3 pg/mL, SDF: 2); Human Interleukin-6 Platinum ELISA kit (BMS213/2, Affymetrix, San Diego, USA; SR: 1.56–100 pg/mL; sensitivity: 0.92 pg/mL, SDF: 2); and Human alpha-2-macroglobulin ELISA kit (K6610, ImmunDiagnostik, Bensheim-Germany; SR: 70–5000 pg/mL; sensitivity: 58 pg/mL, SDF: 2000) were used for measuring the levels of investigated parameters from serum samples by the ELISA method according to the manufacturers' protocols.

2.3. Statistical analysis

All samples and standards were measured in duplicates. Blank and at least 8 standards were included in each ELISA assay. Any result that exceeds 10% inter-run coefficient of variation was repeated. IL-1α, IL-1β, IL-6 and α_2M concentrations were calculated using standard curves (IL-1α $R^2 = 0.9968$; IL-1β $R^2 = 0.9951$; IL-6 $R^2 = 0.9932$; α_2M $R^2 = 0.9997$) and diluted samples were multiplied with dilution factor to determine final concentration. Raw data for each group was analyzed using the GraphPad InStat DTCG 3.06.

The statistical methods used for comparison of groups and correlations were done as previously defined (Gezen-Ak et al., 2013).

Multiple regression analysis to compare the significant contribution of the variable parameters to the constant parameter was also performed. Any positive data in multiple regression analysis was repeated with correlation (Pearson's) analysis in order to keep the most of the data available given that multiple regression excludes any patients with missing data. Probability values lower than 0.05 were considered statistically significant.

3. Results

3.1. Serum levels

The serum IL-1α levels significantly decreased in the EOAD patients (n: 21) compared with their age-matched controls ($p < 0.05$) (Fig. 1A). Similarly, the serum IL-1α levels of the LOAD patients (n: 46) were significantly lower than their age-matched controls or the MCI patients ($p < 0.05$) (Fig. 2A). The serum IL-1α levels of the PD patients (n: 33) were also significantly lower than their age-matched controls or the MCI patients ($p < 0.05$) (Fig. 2A).

The serum IL-1β levels significantly increased in the EOAD patients (n: 19) compared with their age-matched controls ($p < 0.05$) (Fig. 1B). The serum IL-1β levels of the PD patients (n: 39) were significantly higher than those of the age-matched controls and the LOAD or MCI patients ($p < 0.01$, $p < 0.001$, $p < 0.001$, respectively) (Fig. 2B).

The serum IL-6 levels significantly increased in the EOAD patients (n: 16) compared with their age-matched controls ($p < 0.05$) (Fig. 1C). The serum IL-6 levels of the PD patients (n: 40) were

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