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Cerebrospinal Fluid Concentration of Interleukin-6 and Interleukin-10 in Idiopathic Intracranial Hypertension

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The aim of investigation was to determine interleukin-6 (IL-6; a proinflammatory cytokine) and IL-10 (an anti-inflammatory cytokine) concentrations in cerebrospinal fluid (CSF) of Idiopathic Intracranial Hypertension patients (IIH). The study covered 28 middle aged female (IIH patients, n = 14; controls, n = 14). CSF IL-6 and IL-10 concentration were determined by the use of commercial enzyme-linked immunosorbent assay (ELISA) kits. Concentration of IL-6 and IL-10 in CSF of IIH patients was 23.6 ± 3.46 pg mL⁻¹ and 3.7 ± 0.5 pg mL⁻¹ and in controls was 1.8 ± 1.9 and 4.0 ± 1.0 pg mL⁻¹, respectively. Elevated IL-6 concentration in IIH patients found to be statistically significant in comparison to controls ($p < 0.05$). There was no significant difference of IL-10 in IIH and controls. Role of immune system and inflammatory processes in etiology and pathogenesis of IIH must be taking into account.

Key words: Cytokine, idopathic intracranial hypertension, interleukin

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INTRODUCTION

Idiopathic Intracranial Hypertension (IIH) or *Pseudotumor cerebri* is a disorder characterized by symptoms and signs of a space-occupying intracranial mass but with no evidence of a mass or ventricular obstruction on neuroimaging. Lumbar puncture reveals elevated intracranial pressure, but cerebrospinal fluid components are normal. IIH is eight times more prevalent in women. Visual manifestations of IIH are significant and if the disease is not diagnosed or treated lead to blindness (Malomo *et al.*, 2006). Some reported conditions associated with IIH are anatomic, endocrine and nutritional disorders (Wall, 1990) but its etiology (as its name shows) is not known. There is still no consensus about the pathogenesis of IIH. Cytokines are proteins which act as the immune system hormones and have immunomodulatory and neuromodulatory effects (Kronfel and Remic, 2000), hence, they may take part in etiology and pathogenesis of IIH. In some of diseases such as Alzheimer, multiple sclerosis, systemic lupus erythematus, schizophrenia, normal pressure hydrocephalus, multi-infarct dementia and schizophrenia immune system evaluated by measuring concentration of cytokine (Cacoblosor *et al.*, 1991; Garver *et al.*, 2003; Stelmasiak *et al.*, 2000; Komura *et al.*, 2002). No such study is accomplished in IIH, therefore, we measure concentration of IL-6, a proinflammatory cytokine, acts as immune system stimulant and IL-10, an anti-inflammatory cytokine, is an inhibitor of immune system responses in patients with IIH.

MATERIALS AND METHODS

This study was performed on 28 middle aged female patients (age = 20-45 years, mean = 31.3) who were admitted to Neurosurgery Department of Bahonar Hospital (Kerman, Iran) from 2003 to 2007. Among all referred patients (N = 40), 14 IIH patients selected (experiment group) based on modified Dandy criteria (Friedman and Jacobson, 2002). None of the patients had undergone lumbar puncture before, cellular contents of fluid were normal in all of them and they have never undergone any medical treatments or surgery. None of patients had any background or concurrent diseases. Pregnant and obese patients and who have had any IIH associated conditions or diseases (such as metabolic, nutritional and endocrine diseases) were excluded from study. Magnetic resonance images of brain were unremarkable and cerebral venous sinuses were patent in all selected patients. Cerebrospinal fluid was taken by lumbar puncture (which is necessary for diagnosis of IIH). Tubes containing of CSF were transported in dry ice to

the reference laboratory where the CSF samples kept in minus 70°C and then IL-6 and IL-10 concentrations were assay in duplicate using enzyme-linked immunosorbent assay (ELISA). The mean of the two duplicate assays was reported for each subject. The sensitivity of the assay was reportedly high, as determined by the detection range of 1.562-100 pg mL⁻¹. Using the results from three separate runs of standard concentrations, the inter-assay coefficient of variation (CV) was determined for three different concentration ranges. The 1.5-3.0 pg mL⁻¹ level had a CV of 11.08%, from 6.0 to 25 pg mL⁻¹ the CV was 5.41% and from 50 to 100 pg mL⁻¹ the CV was 3.99%.

IL-6 and IL-10 of 14 patient's CSF (who had no signs or symptoms of IIH, had normal pressure hydrocephalus and or lumbar disc surgery) measured by the same method (control group). Statistical analysis was made between the two groups.

RESULTS AND DISCUSSION

The CSF IL-6 and IL-10 data in the 28 middle aged female patients (IIH, n = 14 and control, n = 14) were assessed. The difference of mean ages was not significant. Comparison of IL-6 and IL-10 concentration values obtained in cerebrospinal fluid of IIH and controls has been shown in Table 1. Elevated IL-6 concentration in IIH patients found to be statistically significant in comparison to controls (p<0.05). There was no significant difference of IL-10 in IIH and controls.

Since one cytokine can modulate the secretion of other cytokines, it seems more useful to examine several cytokines in order to understand any involvement of the cytokine network in disease (Özenci *et al.*, 2000). Therefore, for evaluation of inflammatory and immune system in IIH, we measured CSF concentration of IL-10 as an anti-inflammatory and IL-6 as a pro-inflammatory cytokine. IL-6 was higher in IIH, but difference of IL-10 concentration was not significant in IIH and controls. Initially, interleukin-6 called B-cell stimulatory factor-2 hepatocytestimulating factor hybridoma/plasticytoma growth factor and b-interferon eventually became known as simply IL-6 (Gruol and Nelson, 1997). First described in 1985, IL-6 is now known to be one of the key cytokines that initiates immune response, especially by activating B cells to synthesize antibodies (Muller *et al.*, 2002). The cytokine interleukin-6 (IL-6) is an important mediator of inflammatory and immune responses in the periphery.

Table 1: CSF IL-6 and IL-10 concentration in IIH and control

	Controls	IIH	p-value
IL-6 (pg L ⁻¹)	1.8±1.9	23.6±3.46	p<0.05
IL-10 (pg L ⁻¹)	4.0±1.0	3.7±0.5	p>0.05

Values are Mean±SD

IL-6 is produced in the periphery and acts systemically to induce growth and differentiation of cells in the immune and hematopoietic systems and to induce and coordinate the different elements of the acute-phase response. In addition to these peripheral actions, studies indicate that IL-6 is also produced within the CNS and may play an important role in a variety of CNS functions such as cell-to-cell signaling, coordination of neuroimmune responses, protection of neurons from insult, as well as neuronal differentiation, growth and survival (Kaplin *et al.*, 2005). IL-6 also arises from both the parenchyma and the fiber tracts (corpus callosum, anterior commissure, fimbria, lateral olfactory tract, optic tract, internal capsule and corticospinal tracts within the caudate) of the CNS and can be localized in several neuronal types including pyramidal and granular neurons of the hippocampus, neurons of the habenular nucleus, ventromedial and medial preoptic nuclei of the hypothalamus, cerebellar granular neurons and pyramidal neurons of the cerebral cortex (Schobitz *et al.*, 1993). Its presence in white matter suggests the expression of IL-6 by oligodendrocytes, the CNS cell type responsible for myelination of axons that comprise the fiber tracts (Yan *et al.*, 1992). Paradoxically, IL-6 increases intracellular calcium levels during NMDA-receptor activation, enhancing neurotoxicity and cell death in granular neurons (Qiu *et al.*, 1998). Thus, IL-6 can have both neurotrophic and neurotoxic effects in different neuronal types and at different developmental stages. This dual role that IL-6 appears to play in the CNS may explain the wide range of disorders presently being investigated in regard to CSF IL-6. The source of IL-6 appears to be central, rather than peripheral, since elevated levels of IL-6 in CSF appears before leukocytes migrate into the CNS from the periphery and CSF levels of IL-6 are higher than serum levels (Maes *et al.*, 1995). There has been a destructive potential of elevated levels of IL-6 in the CNS, IL-6 increased during the period immediately following the severe head injury (Is *et al.*, 2007). IL-6 levels in the adult CNS are usually low or undetectable under baseline conditions, but increase dramatically in response to injury, inflammation and CNS disease. TNF- α , IL-1 β and neurotransmitters are among the most important stimulators of IL-6 production from astrocytes and microglia within the CNS (Beck *et al.*, 1998). Transgenic mice that overexpress IL-6 within astrocytes exhibit ataxia, seizures and hind limb paralysis and have extensive neurodegeneration (Miller *et al.*, 1993). Neutralization of CNS IL-6 attenuates traumatic spinal cord injury in rats and is associated with reduced nitric oxidize synthetase activity (Brenner, 1994). Kaplin *et al.* (2005) showed IL-6 levels are selectively and dramatically elevated in the CSF

of transverse myelitis patients. Inflammatory penetration of lymphocytes and macrophages or activated residual cells could be a source of IL-6 synthesized locally (Stelmasiak *et al.*, 2000). According to above data and the results of this study, role of IL-6 in etiology and pathogenesis of IIIH must be taking into account. In present study IL-10 also measured as an anti-inflammatory cytokine. Csuka *et al.* (1999) suggest that IL-10 is predominantly induced intrathecally after severe traumatic brain injury where it may downregulate inflammatory events following traumatic brain damage. In this study, there was no significant difference of IL-10 in CSF of IIIH patients and controls.

CONCLUSION

The results of the current study demonstrate that in IIIH, CSF IL-6 was increased. Significance of IL-6 in IIIH in relation to proposed immune process of the disease and wide participation of this cytokine in the immune and inflammatory reactions seems to be important for etiology and pathogenesis. Immune system in IIIH should be further evaluated by more comprehensive studies. It is obvious that if the role of the immune system clarified, new therapeutic strategies will follow.

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