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IL-15 Is Elevated in Cerebrospinal Fluid of Patients With Alzheimer’s Disease and Frontotemporal Dementia

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ABSTRACT

Interleukin-15 is a novel proinflammatory cytokine. It is produced by activated blood monocytes, macrophages, and glial cells. The objective of our study was to assess the role of interleukin-15 as a marker of increased proinflammatory activity in patients with Alzheimer’s disease and frontotemporal dementia. We measured cerebrospinal fluid interleukin-15 levels in 17 patients with Alzheimer’s disease and 7 patients with frontotemporal dementia in comparison with 17 patients with amyotrophic lateral sclerosis and 15 patients with Parkinson’s disease. Patients with Alzheimer’s disease and frontotemporal dementia had significantly higher cerebrospinal fluid interleukin-15 levels compared with patients with noninflammatory neurological diseases ($P < .05$ and $P < .01$, respectively). In Alzheimer’s disease, a significant positive correlation was noted between interleukin-15 levels and age of onset ($R = .48, P = .05$). Our findings suggest that interleukin-15 may be implicated in the pathophysiology of Alzheimer’s disease and frontotemporal dementia. (J Geriatr Psychiatry Neurol 2006;19:114-117)

Keywords: interleukin-15; Alzheimer’s disease; frontotemporal dementia; inflammatory mechanisms

Interleukin (IL)-15 is produced by activated blood monocytes, macrophages, dendritic cells, and activated glial cells. It promotes T-cell proliferation and induction of cytolytic effector cells including natural killer and cytotoxic cells, and it stimulates B cells to proliferate and secrete immunoglobulins.

Alzheimer’s disease (AD) is a neurodegenerative disorder resulting in major cognitive decline. The main pathologic hallmarks are numerous senile plaques, neurofibrillary tangles, and cerebrovascular amyloidosis in various regions of the brain. Aβ amyloid, a protein derived from β-site proteolytic processing of the amyloid precursor protein, is the major component of senile plaques. Inflammatory responses have been implicated in the pathogenesis of AD and deposition of Aβ amyloid. Lesions of AD are associated with low-grade but sustained inflammatory responses. Activated microglia have been demonstrated in pathologic lesions in several neurological diseases including AD. The presence of the acute phase proteins a-1-antichymotrypsin, a-2 macroglobulin, C-reactive protein, and proinflammatory cytokines IL-6 and IL-1 in senile plaques has also been demonstrated. Adhesion molecules are presumably involved in brain tissue lesions of patients with AD. To find out whether IL-15 is involved in the possible inflammatory reactions of AD and other dementias, we measured IL-15 cerebrospinal fluid (CSF) levels in patients with AD and frontotemporal dementia (FTD) compared with CSF IL-15 levels of patients with other noninflammatory neurological diseases like Parkinson’s disease (PD) and amyotrophic lateral sclerosis (ALS).
METHODS

Patients
A total of 69 patients was enrolled in the study, divided in 4 groups: (1) The AD group comprised 25 patients with probable AD, diagnosed according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.22 (2) The FTD group comprised 7 patients with frontotemporal lobar degeneration, diagnosed according to the El Escorial WFN criteria.21 (3) The ALS group comprised 19 patients with probable or definite amyotrophic lateral sclerosis, diagnosed according to the El Escorial WFN criteria.21 (4) The PD group comprised 18 patients with clinically definite Parkinson's disease, diagnosed according to the criteria of Larsen et al.22 None of the studied patients had evidence of systemic inflammation on clinical examination or serum biochemical tests. The PD and ALS groups served as controls for the AD and FTD groups, because PD and ALS have been considered to be noninflammatory neurological diseases (NIND). Patients with AD and FTD did not take any pharmacological treatment during the last 2 months before their admission.

Sample Collection and IL-15 Assay
CSF samples were obtained after informed consent, by lumbar puncture at the L5-S1 interspace, between 10 and 11 AM, after overnight fasting. Samples were centrifuged for removal of cells, and bloody samples were discarded. Following that, samples were immediately frozen at −70°C and thawed only once, just before the assay.

CSF concentrations of circulating IL-15 were measured by immunoassay using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). CSF samples diluted 1:3 were added in duplicate to microtiter wells and assayed according to routine procedures. Optical densities were determined by means of a micro-ELISA reader (LP 400, Pasteur Diagnostics). Values were calculated by comparison with a standard curve that was generated with IL-15 standards. The limit of detection was 2 pg/mL.

Statistical Analysis
All variables were tested for normality and homogeneity of variances by the Shapiro-Wilks's and Levene's tests, respectively. Some deviations from normality were noted and variances were heterogeneous. However, logarithmic transformation restored the above violations and permitted the use of analysis of covariance (ANCOVA), with diagnostic group and sex as factors and age as a covariate, for comparison of IL-15 levels among groups. Correlation of IL-15 with age, age of onset, disease duration, Mini-Mental State Examination (MMSE) score, and rate of dementia progression was also tested separately in each group by Spearman's rank correlation coefficient ($r_s$). The rate of dementia progression was calculated in AD and FTD groups using the formula $(30 – \text{MMSE}/\text{disease duration})$. The level of statistical significance was set at .05.

RESULTS

Demographic and biochemical data are summarized in Table 1. Some differences in respect to sex and age among the studied groups were noted; however, none reached statistical significance. Furthermore, age, sex, disease duration, and MMSE score did not affect IL-15 levels in any of the groups. Rate of dementia progression did not affect IL-15 levels in AD and FTD. ANCOVA revealed a significant effect of diagnostic group (but not sex or age) on IL-15 levels ($P < .01$). Patients with AD and FTD had significantly increased CSF IL-15 levels compared with the ALS and PD groups. The ALS and PD groups did not differ between each other. Levels in FTD were higher than in AD. In AD, a significant positive correlation was noted between IL-15 levels and age of onset ($r_s = .82, P < .01$).

DISCUSSION

In the present study we investigated CSF levels of IL-15 as a potential marker of immune reactions in patients with AD and FTD. Patients with AD had elevated IL-15 concentrations compared with NIND patients. However, other studies on circulating levels of cytokines in CSF of AD patients were not conclusive and had conflicting results.23,24 This may suggest that the production and action of cytokines are localized in the central nervous system parenchyma, not allowing a representative detection in CSF.23 Based on the inflammatory hypothesis, several anti-inflammatory drugs are in development for the treatment of AD, and several clinical trials with anti-inflammatory drugs in AD patients have been carried out.25-27

Except for some hereditary cases, the causes of FTD are largely unknown; however, an involvement of t-tau and/or neurofilament proteins in the mechanisms of the disease has been suggested.28,29 It is not known whether autoimmune mechanisms are in any way involved in FTD pathophysiology. Inflammatory processes have been suggested,30,31 but thorough investigations have not been carried out yet. Significantly increased CSF levels of tumor necrosis factor-$\alpha$ and transforming growth factor-$\beta$ have been
observed in FTD patients compared with controls.\textsuperscript{32} In our study, CSF IL-15 levels in FTD patients were higher than in NIND patients. These results may be compatible with involvement of proinflammatory cytokine activation during the neurodegenerative process of FTD.

In our study, CSF IL-15 concentrations in AD patients were positively correlated with age of onset. Our findings may suggest that in senile dementia of AD type, cellular and humoral immune responses might have a stronger implication concerning presenile dementias. No correlations between disease duration or MMSE scores and CSF IL-15 concentrations were revealed in any studied group of patients. It is obvious that more comprehensive clinical trials need to be carried out before firm conclusions can be drawn concerning impaired cytokine central and peripheral release and clinical conditions of AD patients.

To our knowledge this is the first study in which CSF IL-15 concentrations were assessed in patients with neurodegenerative disorders such as AD and FTD. Weaknesses of our study are the small number of FTD patients and the lack of a group including healthy participants. Another weakness is the inexact correlation between CSF IL-15 or other cytokines levels and neurodegenerative neurological disease.

Table 1. Demographic and Clinical Data of the Studied Groups

<table>
<thead>
<tr>
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<th>ALS</th>
<th>PD</th>
<th>AD</th>
<th>FTD</th>
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<tbody>
<tr>
<td>n (males/females)</td>
<td>19 (6/13)</td>
<td>18 (10/8)</td>
<td>25 (7/18)</td>
<td>7 (3/4)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>61 ± 9</td>
<td>56 ± 12</td>
<td>64 ± 11</td>
<td>58 ± 12</td>
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<tr>
<td>Disease duration, mean ± SD</td>
<td>1.8 ± 1</td>
<td>2.7 ± 1.4</td>
<td>2.7 ± 1.8</td>
<td>2 ± 1.8</td>
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<tr>
<td>MMSE, median (25th-75th percentile)</td>
<td>28 (27-29)</td>
<td>27 (26-28)</td>
<td>19 (12-22)</td>
<td>21 (14-23)</td>
</tr>
<tr>
<td>IL-15, pg/mL, adjusted mean ± SD</td>
<td>0.85 ± 0.22</td>
<td>0.88 ± 0.25</td>
<td>1.09 ± 0.26\textsuperscript{b}</td>
<td>1.38 ± 0.49\textsuperscript{b}</td>
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Note: ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; AD, Alzheimer's disease; FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination.

References


