Background
In addition to extracellular Aβ deposition and intraneuronal accumulation of phosphorylated tau, chronic inflammation could be an important contributor to early stages of AD pathophysiology. Numerous inflammatory molecules in the blood and CSF have been investigated to discover novel biomarkers and clarify the inflammatory processes involved in AD. To our knowledge, however, few studies have examined the relationship between CSF cytokine levels and cortical Aβ deposits.

Aim
The aim of the present study was to determine whether cytokine levels in the CSF correlate with PiB retention.

Methods

Participants
A total of 33 MCI subjects (same as J-ADNI criteria) 65-86 y.o. Subjective memory complaints and objective memory impairment. Mini Mental State Examination (MMSE) score of 24-30. Impairment of education-adjusted score in delayed recall of logical memory in WMS-R. Clinical Dementia Rating score of 0.5. Absence of significant impairment in cognitive function or activities of daily living.

Cytokine multiplex assay
Lumbar puncture was performed in the L3/4 or L4/5 interspace. CSF (10 mL) was collected in a tube and centrifuged at 1500 g for 10 min at room temperature. Aliquots of the supernatant were immediately frozen and stored at -80°C. The concentrations of 48 cytokines in the CSF were simultaneously measured using the Bio-Plex 200 suspension array system (Bio-Rad, Hercules, CA, USA) with the Bio-Plex Manager Software version 6.0, using microsphere-based multiplex assays. We used the Bio-Plex Pro Human Cytokine 27-plex (MSDKC0AFY, Bio-Rad) and 21-plex panels (MF0005KMII; Bio-Plex).

Positron emission tomography scans
Static 11C-PiB PET studies were acquired using the Siemens Biograph mCT40 (Siemens Medical Solutions, Inc., Knoxville TN, USA) in three-dimensional scanning mode. Each patient was injected intravenously with a bolus of 11C-PiB (55 ± 185 MBq) followed by a saline flush. PET scans were carried out for 20 min, providing 110 slices with 1.5 mm thickness that covered the entire brain.

Calculating SUVR-value
PiB PET scans were spatially normalized to a customized PiB-PET template in the Montreal Neurological Institute reference space using Statistical Parametric Mapping 8 (Wellcome Trust Center for Neuroimaging, London, UK). The region of interest (ROI) analysis was carried out using MarsBar. PiB uptake was assessed based on a standardized uptake value ratio (SUVR), which is calculated by dividing the 11C-PiB retention level in a particular ROI by the ROI value in the cerebellar hemispheres. Mean cortical SUVR was expressed as the average SUVR of the mean of the frontal lobes, parietotemporal lobes and posterior cingulate regions. An SUVR cut-off of 1.4 was used to classify the participants into the PiB-positive or PiB-negative subgroups.

Results

Clinical and demographic characteristics of Pittsburgh compound B-positive and Pittsburgh compound B-negative mild cognitive impairment patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PiB positive MCI</th>
<th>PiB negative MCI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.56 ± 5.24</td>
<td>76.47 ± 4.69</td>
<td>0.95</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.33 ± 1.41</td>
<td>10.67 ± 2.23</td>
<td>0.22</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.00 ± 1.68</td>
<td>24.20 ± 2.08</td>
<td>0.53</td>
</tr>
<tr>
<td>NMS-R II</td>
<td>5.94 ± 2.50</td>
<td>6.07 ± 3.20</td>
<td>0.22</td>
</tr>
<tr>
<td>SUVR</td>
<td>1.83 ± 0.37</td>
<td>1.06 ± 0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t-tau</td>
<td>151.12 ± 74.30</td>
<td>112.18 ± 60.43</td>
<td>0.09</td>
</tr>
<tr>
<td>p-tau</td>
<td>42.02 ± 14.35</td>
<td>27.20 ± 14.50</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD. The q-test for sex distribution and the Mann–Whitney U-test for others. A p-value <0.05 was considered statistically significant.


Correlation analysis between cytokines and Pittsburgh compound B retention

Aim
The Mann–Whitney U-test. A p-value <0.05 was considered statistically significant for correction for multiple comparisons, a p-value <0.05 was considered statistically significant.


Discussion

Aβ induces MIP-1β in vitro, and APP/PS1 transgenic mice overexpress MIP-1β and CCR5 in activated astrocytes surrounding Aβ plaques (J Neuropathol Exp Neurol 2014). Furthermore, activated microglia promote the accumulation of intraneuronal Aβ in brains infected with HIV (J Neuromucosal Pharmacol 2009), and MIP-1β is involved in the progression of AIDS (Plos Genet 2014). These findings lead us to suspect that Aβ protein might produce MIP-1β through the activation of astrocytes and microglia. Few studies have examined the relationship between the CSF SCGF levels and cortical amyloid deposits. It is unclear why SCGF-β levels significantly correlated with PiB retention in only the PiB-negative subgroup.

Conclusion

The findings of the present study showed a significant correlation between CSF SCGF levels and PiB retention in the PiB-negative subgroup, and between CSF SCGF-β levels and PiB retention in the PiB-negative subgroup.