IV. 4. Relationship between Cerebral Glucose Metabolism and CSF Markers in Neurodegenerative Dementia


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Introduction

Amyloid-β peptide (Aβ) and microtubule-associated protein tau are two principal molecules that constitute the pathological hallmarks of AD, i.e. senile plaques and neurofibrillary tangles. Cerebrospinal fluid (CSF) assays showing elevation in levels of tau (CSF-tau) and reduction in levels of Aβ ending at amino acid position 42 (CSF-Aβ1-42) have suggested them to be the most reliable biochemical markers in the diagnosis of AD at the present time (For more details, see Consensus report). Moreover, recent reports have demonstrated that a combinatorial analysis of CSF-tau and CSF-Aβ1-42 may provide a more accurate diagnostic strategy for the diagnosis of AD. Although these biological markers are potentially useful to aid in the diagnosis of AD, it is not clearly understood if these molecules in CSF reflect fundamental features of neuron dysfunction or synapse loss in the AD brain. Furthermore, elevation of the CSF-tau levels and reduction of the CSF-Aβ1-42 levels are frequently observed in patients with non-AD neurodegenerative dementias including dementia with Lewy bodies (DLB), fronto-temporal dementia (FTD), corticobasal degeneration (CBD) and Creutzfeldt-Jakob disease (CJD). On the other hand, functional imaging techniques, including positron emission tomography (PET), have been used and accepted as methods to assess functional abnormalities in central nervous system disorders. In particular, cerebral glucose metabolism measured by PET and 2-[18F] fluoro-2-deoxy-D-glucose (FDG) provides unique and quantitative functional data that might explain a regional distribution of neuron death and synaptic dysfunction in AD brain. In order to get more insights into the clinical usefulness of the analysis of CSF-tau and CSF-Aβ1-42 as measures to monitor neurodegenerative processes of the brain, we quantified the CSF levels of these molecules in AD and non-AD patients, and these data were compared with cerebral glucose metabolic ratios measured by FDG-PET.

Patients and Methods

Fifteen patients with "probable AD" (69±7 years, M/F=6/9) and nine patients with
other neurodegenerative diseases (62±7 years, M/F=5/4) including DLB (n=4), FTD (n=3), CBD (n=1) and CJD (n=1) were examined. The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria\(^{12}\). The diagnosis of other neurodegenerative diseases was performed according to the consensus guidelines proposed by McKee et al. for DLB\(^{13}\), the criteria by the Lund and Manchester groups for FTD\(^{14}\) and the original description by Gibb et al. for CBD\(^{15}\). All patients underwent extensive neurological and neuroimaging studies as well as laboratory examinations to exclude other possible causes of dementia. Dementia severity was assessed by Mini-Mental State Examination (MMSE) within 3 month intervals of PET/CSF examination. The MMSE scores in AD patients were 19.1±5.4 points (range 5-26 points), and duration of the disease was 3.7±3.4 years (range 1.5-13 years). In the non-AD patients, the MMSE scores were 16.8±7.0 points (range 6-27 points) and duration of the disease was 2.2±1.0 years (range 0.5-4 years).

CSF was taken into sterile polypropylene tubes by lumbar puncture. CSF-\(A\beta\) ending at amino acid position 42 was quantified by a sandwich enzyme-linked immunosorbent assay (ELISA) using two end-specific antibodies (21F12 and 3D6)\(^{16}\). Total tau in CSF was quantified by another sandwich ELISA (INNOTEST hTauAg, Innogenetics, Belgium) as previously described\(^{6,17}\).

Cerebral glucose metabolism with FDG was measured using an ECAT PT931 (CTI Inc, Knoxville, TN, USA) tomograph. Following a \(^{68}\)Ge/Ga transmission scan of 7 min duration, an emission scan was performed for about 60 min after intravenous injection of FDG. Arterial blood sampling was performed from the radial artery during the scan, and the cerebral metabolic rate of glucose (CMRglu) was calculated by an autoradiographic method using an input function obtained by the measurement of plasma radioactivity. The global glucose metabolism was defined as an average CMRglu value over both gray and white matter structures of 5 slices. ROIs were placed on individual PET images in the cerebellar hemisphere, superior and inferior frontal cortices, superior and inferior temporal cortices, parietal, occipital, medial temporal, striatum and thalamus, referring to the individual magnetic resonance images. The global and regional to cerebellar ratio (global and regional metabolic ratio) was determined to eliminate individual variance of activity. Correlations of the glucose metabolic ratio with the CSF-\(A\beta1-42\) and CSF-tau levels were assessed by Pearson’s simple correlation methods. Multiple regression analysis was performed to eliminate the effect of age on global and regional glucose metabolism.

**Results**

The mean levels of CSF-\(A\beta1-42\) and CSF-tau were 322.0±118.2 pg/ml and 82.2±49.8 pg/ml in the AD group, and 356.0±239.0 pg/ml and 53.2±33.7 pg/ml in the non-AD group. The MMSE scores in the AD patients showed a trend toward decreasing with decreasing CSF-\(A\beta1-42\) levels. A simple correlation analysis demonstrated that the CSF-
Aβ1-42 levels in the AD patients had a significant and positive correlation with the global metabolic ratio (r=0.647, p=0.008). Notably, in the analysis of non-AD patients, the CSF-Aβ1-42 levels also significantly correlated with the global glucose metabolic ratio (r=0.896, p=0.0004) (Figure). However, there was no consistent correlation between the CSF-tau levels and the global metabolic ratios in either AD or the non-AD group. Results obtained by multiple regression analysis adjusted by age further demonstrated that the CSF-Aβ1-42 levels independently correlated with the global metabolic ratios in both the AD group (p=0.010) and the non-AD group (p=0.001). In particular, the CSF-Aβ1-42 levels in the AD patients significantly correlated with regional metabolic ratio in the ROI of the inferior temporal cortex (r=0.479, p=0.048). In other areas, no significant correlation was observed between the regional metabolic ratio and the CSF-Aβ1-42 levels in the ROI analysis (Table) (For further details, see Ref 18).

**Discussion**

Despite a small sample size, this study is the first to describe a positive and strong correlation between CSF-Aβ1-42 levels and PET measures of cerebral glucose metabolism in AD. At the beginning of the present study, we hypothesized that we might see a negative correlation between CSF-tau levels and the PET measures of cerebral glucose metabolism since numerous studies have demonstrated that the CSF-tau levels are elevated in AD probably due to a progressive and massive death of neurons3-7. Instead, we found that the CSF-Aβ1-42 levels, but not the CSF-tau levels, had a positive correlation with brain metabolism, and this correlation was most significant in the temporal region. Our finding that the positive correlation between the CSF-Aβ1-42 and the global cerebral glucose metabolism in AD naturally leads us to assume that the CSF-Aβ1-42 levels might be high in the early stages of AD followed by a decline as the disease progresses. Indeed, there was a trend between MMSE scores and CSF-Aβ1-42 levels in our limited number of patients, and another recent study also demonstrated the relationship between CSF-Aβ1-42 and MMSE scores in a larger sample size of AD patients19. Further, a longitudinal study demonstrated that the CSF-Aβ1-42(43) levels continuously declined during a follow-up in AD patients7. Taken these results together, it is likely that CSF-Aβ1-42 levels may decline as AD becomes more severe. To further clarify the relationship between the CSF-Aβ1-42 levels and the disease severity, it is necessary to examine temporal changes in the CSF-Aβ1-42 levels and in the PET measures of brain metabolism by a longitudinal analysis.
Reference


Table 1. Regression parameters and determination coefficients for regional metabolic ratio.

<table>
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<tr>
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<th>CSF-Aβ42</th>
<th>Age</th>
<th>R²</th>
</tr>
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<tbody>
<tr>
<td>inferior frontal</td>
<td>0.267</td>
<td>-0.507</td>
<td>0.335</td>
</tr>
<tr>
<td>superior frontal</td>
<td>0.337</td>
<td>-0.594</td>
<td>0.476*</td>
</tr>
<tr>
<td>inferior temporal</td>
<td>0.479*</td>
<td>-0.440</td>
<td>0.433*</td>
</tr>
<tr>
<td>superior temporal</td>
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<td>0.026</td>
<td>0.050</td>
</tr>
<tr>
<td>parietal</td>
<td>0.123</td>
<td>0.166</td>
<td>0.042</td>
</tr>
<tr>
<td>occipital</td>
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<td>0.231</td>
<td>0.105</td>
</tr>
<tr>
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<td>0.082</td>
<td>0.108</td>
</tr>
<tr>
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<td>-0.241</td>
<td>0.019</td>
</tr>
<tr>
<td>thalamus</td>
<td>0.364</td>
<td>-0.304</td>
<td>0.230</td>
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* p < 0.05
Figure 1. Correlation between CSF levels of Aβ1-42 and the global glucose metabolic ratio in fifteen AD and nine non-AD patients.