Laboratory Examinations Correlated with Severity of Dementia*

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ABSTRACT

Acetylcholine esterase, α1-antichymotrypsin, homovanillic acid (HVA), 3-methoxy-4-hydroxy-phenylenglycol (MHPG), norepinephrine, dopamine, 5-hydroxy-indolacetic acid (5-HIAA), and γ-aminobutyric acid (GABA) in the serum and cerebrospinal fluid (CSF) were quantified. Positive wave with the latency about 300 msec (P300) and electroencephalography (EEG) were examined in 10 patients with Alzheimer’s disease, 10 patients with vascular dementia, and 10 age-matched healthy controls. Serum α1-antichymotrypsin concentrations were significantly higher in the Alzheimer’s disease group than in the vascular dementia and healthy control groups. Homovanillic acid concentrations in CSF were significantly lower in the vascular dementia group than in the Alzheimer’s disease and the healthy control groups. A significant positive correlation was present between the mini-mental state examination (MMSE) score (normal range of 24 to 30) and the acetylcholine esterase concentration in the CSF. Significant negative correlations were present between the MMSE score and the P300 latency, between the MMSE score and the MHPG concentration in the CSF, between the MMSE and the norepinephrine concentration in the CSF, and between the MMSE score and the dopamine concentration in the CSF.

Introduction

Several laboratory examinations such as acetylcholine esterase,1.2.3.4.5 α1-antichymotrypsin,6.7.8 homovanillic acid (HVA),3.9 3-methoxy-4-hydroxy-phenylenglycol (MHPG),10 norepinephrine10 and P30011,12 have been reported to be abnormal in ischemic dementia and Alzheimer’s disease. However, it is not known by us which of these analytes is the most specific for Alzheimer’s disease nor which of these examinations shows the closest correlation with the severity of dementia. Therefore, these examinations were performed in Alzheimer’s dis-
TABLE I
Characteristics of Subjects in Three Groups

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s Disease</th>
<th>Vascular Dementia</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>66.3 ± 9.2</td>
<td>67.4 ± 8.7</td>
<td>66.7 ± 8.9</td>
</tr>
<tr>
<td>Male:female</td>
<td>3:7</td>
<td>4:6</td>
<td>3:7</td>
</tr>
<tr>
<td>Duration of illness (years)*</td>
<td>3.5 ± 1.8</td>
<td>4.2 ± 2.3</td>
<td>—</td>
</tr>
<tr>
<td>Mini-mental state examination (score)*</td>
<td>17 ± 5</td>
<td>18 ± 6</td>
<td>30 ± 1</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

Materials and Methods

Ten patients with Alzheimer’s disease, 10 patients with vascular dementia, and 10 age-matched healthy controls were studied with their informed consent. The diagnosis of Alzheimer’s disease and vascular dementia was made according to the diagnostic criteria. The diagnosis was made by two neurologists using history, physical, and neurological examinations, head computed tomography and head magnetic resonance imaging. In table I are shown characteristics of the subjects in the three groups. The patients were admitted to our hospital, and head magnetic resonance imaging, blood tests, lumbar puncture, positive wave with latency about 300 msec (P300), electroencephalography and mini-mental state examination (MMSE) were performed on all patients. Serum and CSF acetylcholine esterase were quantified with the Analyzer 7250.* Serum and CSF levels of α1-antichymotrypsin, HVA, MHPG, norepinephrine, dopamine, 5-hydroxyindolacetic acid and γ-aminobutyric acid were examined in the Special Reference Laboratories (SRL).†

The P300 was measured according to the guideline of the Japan Society of Electroencephalography and Electromyography with a Synax 1100 evoked potential recorder.‡ The cerebral potentials were recorded from electrodes at Fz, Cz, and Pz referenced to linked earlobes. The electro-oculogram was recorded, and trials with a large electro-oculogram potential were autorejected. The filter bandpass was set at 0.5 to 100 Hz, and the analysis window was set from 160 msec prestimulus till 640 msec poststimulus. An oddball stimulus paradigm was employed in which subjects kept a running mental count of rare target tone pips (p = 0.2, 2,000 Hz) interspersed against a background of more frequent nontarget tone pops (p = 0.8, 1,000 Hz). Signals were amplified 50,000 times and averaged separately according to rare and frequent tones. Thirty responses to rare tones were averaged and two averages

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were obtained to ensure reproducibility. The P300 latency and amplitude were measured at Pz.

Statistical analysis was performed using Mann-Whitney's U test for comparison among the three groups and using Spearman's correlation coefficients for correlation between the laboratory examination and the mini-mental state examination (MMSE).

Results

In table II are shown the results of laboratory examinations. Serum α1-antichymotrypsin concentration was significantly higher in the Alzheimer's disease group than in the vascular dementia and healthy control groups. Homovanillic acid concentration in the CSF was significantly lower in the vascular dementia group than in the Alzheimer's disease and healthy control groups. A significant positive correlation was present between the MMSE score and the acetylcholine esterase concentration in the CSF. Significant negative correlations were present between the MMSE score and the P300 latency, between the MMSE score and the MHPG concentration in the CSF, and between the MMSE score and the norepinephrine concentration in the CSF.

No significant differences were present concerning 5-hydroxy-indolacetic acid, γ-aminobutyric acid, and background activity in electroencephalography.

Discussion

It is sometimes difficult to distinguish early Alzheimer's disease and normal cognitive aging by clinical assessment, and biochemical markers are sorely needed for this differential diagnosis. Laboratory examinations were selected which were reported to be abnormal in dementia and could be done in our hospital or related laboratories.

The MMSE has been used extensively by clinicians and researchers as a screening instrument for cognitive impairment. According to the MMSE score, the severity of dementia may be classified into mild (>21), moderate (20 to 11), and severe (10 to 0) dementia. The severity of dementia in our cases was moderate because the mean scores of the MMSE in the Alzheimer's disease group and the vascular dementia group were 17 and 18, respectively.

In the present study, α1-antichymotrypsin concentration in the serum was significantly higher in the Alzheimer's disease group than in the vascular dementia and healthy control group, but α1-antichymotrypsin concentration in the CSF did not show any significant difference among the three groups. This is considered to be due to the fact that α1-antichymotrypsin concentration in the CSF was too low to be detected in some subjects. Considering the reports that α1-antichymotrypsin is intimately associated with β peptide in the filamentous amyloid deposits of Alzheimer's disease, high α1-antichymotrypsin concentration in the Alzheimer's disease group may be related with the pathogenesis of Alzheimer's disease.

In the present study, concentration of HVA in the CSF was significantly lower in the vascular dementia group than in the Alzheimer's disease and healthy control groups. Although concentration of HVA in the CSF in dementia is controversial, our results are consistent with the report that it was decreased in stroke and multi-infarct dementia and also the report that it was normal in Alzheimer's disease.

Acetylcholinesterase concentration in the CSF has been reported to be decreased in Alzheimer's disease. The P300 is considered to reflect cogni-
### TABLE II

Results of Laboratory Examinations
Comparison Among Groups and Correlation Coefficients with Mini-mental State Examination Score

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer's Disease Group</th>
<th>Vascular Dementia Group</th>
<th>Healthy Control Group</th>
<th>Correlation Coefficients with MMSE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine esterase (mg/dl)</td>
<td>16.5 ± 5.2^a</td>
<td>18.3 ± 4.6^a</td>
<td>25.4 ± 4.8</td>
<td>0.45^b</td>
</tr>
<tr>
<td>α1-Antichymotrypsin (mg/dl)</td>
<td>0.35± 0.2</td>
<td>0.28± 0.2</td>
<td>0.20± 0.1</td>
<td>-0.19</td>
</tr>
<tr>
<td>Homovanillic acid (ng/ml)</td>
<td>39.2 ± 6.7</td>
<td>27.6 ± 6.4</td>
<td>42.3 ± 5.9</td>
<td>0.28</td>
</tr>
<tr>
<td>MHPG (ng/ml)</td>
<td>19.5 ± 4.5^a</td>
<td>18.6 ± 5.2^a</td>
<td>11.3 ± 4.6</td>
<td>-0.41^b</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>203.8 ± 43.6^a</td>
<td>195.2 ± 51.6^a</td>
<td>63.5 ± 28.2</td>
<td>-0.49^d</td>
</tr>
<tr>
<td>5-Hydroxy–indolacetic acid (ng/ml)</td>
<td>15.3 ± 8.4</td>
<td>13.5 ± 9.3</td>
<td>21.5 ± 7.1</td>
<td>0.26</td>
</tr>
<tr>
<td>γ-Aminobutyric acid (ng/ml)</td>
<td>498.3 ± 89.2</td>
<td>523.8 ± 94.2</td>
<td>557.3 ± 97.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine esterase (mg/dl)</td>
<td>23.5 ± 6.5</td>
<td>22.5 ± 5.8</td>
<td>28.4 ± 6.1</td>
<td>0.21</td>
</tr>
<tr>
<td>α1-Antichymotrypsin (mg/dl)</td>
<td>41.5± 5.9^a</td>
<td>30.8 ± 6.8</td>
<td>29.4 ± 4.8</td>
<td>-0.24</td>
</tr>
<tr>
<td>Homovanillic acid (ng/ml)</td>
<td>25.6 ± 5.6</td>
<td>27.4 ± 5.9</td>
<td>31.6 ± 5.1</td>
<td>0.19</td>
</tr>
<tr>
<td>MHPG (ng/ml)</td>
<td>14.8 ± 4.1</td>
<td>13.3 ± 4.8</td>
<td>10.9 ± 5.3</td>
<td>-0.21</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>126.4 ± 72.1</td>
<td>118.2 ± 68.6</td>
<td>61.3 ± 42.5</td>
<td>-0.23</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>75.3 ± 45.6</td>
<td>73.6 ± 42.6</td>
<td>23.5 ± 18.6</td>
<td>-0.18</td>
</tr>
<tr>
<td>5-Hydroxy–indolacetic acid (ng/ml)</td>
<td>5.89± 2.1</td>
<td>6.45± 3.1</td>
<td>7.28± 1.9</td>
<td>0.17</td>
</tr>
<tr>
<td>γ-Aminobutyric acid (ng/ml)</td>
<td>145.2 ± 51.3</td>
<td>158.4 ± 48.6</td>
<td>203.3 ± 45.6</td>
<td>0.18</td>
</tr>
<tr>
<td>P300 latency (msec)</td>
<td>403.0 ± 25.0^a</td>
<td>397.0 ± 28.0^a</td>
<td>321.0 ± 18.0</td>
<td>-0.40^b</td>
</tr>
<tr>
<td>Electroencephalography (Hz)</td>
<td>6.9 ± 1.8</td>
<td>7.2 ± 1.7</td>
<td>8.1 ± 1.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

^a P < 0.05 versus healthy control group.
^b P < 0.01 versus healthy control group and P < 0.05 versus Alzheimer's disease group.
^c P < 0.01 versus healthy control group and P < 0.05 versus vascular dementia group.
^d P < 0.01.
^e P < 0.01 versus healthy control group and P < 0.05 versus Alzheimer's disease group.

Both MHPG and norepinephrine concentrations in the CSF have been reported to be increased in Alzheimer's disease. Currently, a significant positive correlation was present between the MMSE score and the acetylcholine esterase concentration in the CSF. Significant negative correlations were present between the MMSE score and the P300 latency, between the MMSE score and the MHPG concentration in the CSF, between the MMSE score and

tive function, and the P300 latency has been reported to be prolonged in dementia. Both MHPG and norepinephrine concentrations in the CSF have been reported to be increased in Alzheimer's disease. Currently, a significant positive correlation was present between the MMSE score and the acetylcholine esterase concentration in the CSF. Significant negative correlations were present between the MMSE score and the P300 latency, between the MMSE score and the MHPG concentration in the CSF, between the MMSE score and
the norepinephrine concentration in the CSF, and between the MMSE score and the dopamine concentration in the CSF. This suggests that these examinations are not specific for Alzheimer's disease but correlate with dementia.

No significant differences were present concerning 5-HIAA, GABA, and background activity in electroencephalography in the present study. These examinations are considered to be controversial.4,9,19

Although our results should be considered preliminary until a greater number of Alzheimer's disease patients are studied, it is our belief that α1-antichymotrypsin is a possible biochemical marker for Alzheimer’s disease. Our recommendation is that α1-antichymotrypsin concentration should be determined in the serum of patients with suspected Alzheimer's disease.

References

19. Ma J, Yee A, Brewer B Jr, Das S, Potter H. Amy­loid-associated proteins α1-antichymotrypsin


