Blood-brain barrier (BBB) permeability in the demented elderly was investigated by use of the ratio of cerebrospinal fluid (CSF) albumin (Alb) to serum Alb (Q-Alb). Subjects with Alzheimer type dementia (AD), vascular dementia (VD), and controls without dementia (C) were investigated. Patients with AD were divided into mild AD (mAD) and severe AD (sAD) by the use of Hasegawa’s dementia scale. The Q-Alb and the ratio of CSF α1-antichymotrypsin (ACT) to serum ACT (Q-ACT) were evaluated. Correlations between Q-Alb and Q-ACT were compared among the groups (mAD, sAD, VD, C). Correlations between Q-Alb and major monoaminergic neurochemicals were also analyzed. It was suggested that BBB permeability was preserved in C group, while it was impaired in the patients with VD. In AD group it appeared to be rather well preserved in mAD, while it seemed to be disturbed in a graded manner according to the progression of dementia.

Key words: senile dementia, α1-antichymotrypsin, monoamines, correlation

Introduction

Recent progress of research on senile dementia of the Alzheimer type (AD) revealed that there might exist some diagnostic biological markers, such as α1-antichymotrypsin (ACT) in cerebrospinal fluid (CSF) (1). In the previous reports it was shown that the concentrations of ACT in CSF of probable AD were significantly elevated compared with those of controls or patients with other types of dementia (1, 2). It was also shown that the CSF ACT level correlated significantly with the scale of dementia, i.e. Hasegawa’s dementia scale (HDS), implying that ACT might reflect the severity of the intellectual dysfunction. The correlations between ACT levels in CSF or HDS score and concentrations of multiple neurochemicals (catecholaminergic and indoleaminergic) in CSF, such as homovanillic acid (HVA) or the ratio of kynurenine (KYN) to tryptophan (TRP) (KYN/TRP), were also investigated to find several possible diagnostic biological markers reflecting the degree of mental function, as reported previously (2).

In the daily clinics of demented patients, many elderly persons with AD show various atypical symptoms suggesting other etiological diseases of dementia, such as cerebrovascular diseases or inflammatory diseases to which abnormalities of the permeability of the blood-brain barrier (BBB) might be related (3–5).

Several reports have concerned the abnormalities of BBB in cerebral ischemia and vascular dementia (6–10). However, only a few reports have focused on the abnormal permeabilities of BBB in AD. Historically BBB dysfunction in AD was suggested by Wisniewski and Kozlowski (11), and Alafuzoff et al (12), whereas no evidence for abnormal penetration of blood-borne proteins was found in another study by Jonker et al (13). Elovaara et al investigated BBB function and intrathecal protein synthesis by analyzing CSF in AD (14). Scheib et al reported that AD is a form of capillary dementia (15). Blennow et al reported disturbance of the BBB in AD to be related to vascular factors (16). Perlmuter and Chui reported about microangiopathy in relation to vascular basement membrane in AD (17). Harik and Kalaria also reported that BBB abnormalities in AD are due to the microvasculature abnormalities associated with noradrenergic deafferentiation (18). Buee et al reported pathological alterations of cerebral microvasculature in AD and related dementing disorders (19). Mattila and colleagues investigated altered BBB function in AD by analyzing proteins of CSF from AD and vascular dementia (VD) patients, and suggested a high molecular-weight transudate type of...
impaired BBB (20).

In the present report the results of the CSF-serum albumin ratio (Q-Alb) in demented elderly were investigated more in depth. Q-Alb is thought to be a marker of the permeability of the BBB in neuropsychological diseases (21). Kirch et al (22) investigated Q-Alb in schizophrenia and Niklasson and Agren (23) reported on Q-Alb in depression, but their results were not specific to these psychotic diseases. In this report correlations between Q-Alb and CSF-serum ACT ratio (Q-ACT), and the correlations between Q-Alb and concentrations of major monoamine metabolites, 3-methoxy-4-hydroxyphenyl-glycol (MHPG), homovanillic acid (HVA), and 5-hydroxy-indole-3-acetic acid (5-HIAA) in CSF were investigated in attempt to find the abnormal permeabilities of the BBB in dementing diseases. It was highly suggested that BBB permeability is compromised in patients with vascular dementia, while in patients with AD it appeared to be impaired in a graded fashion as the disease advanced. The obtained results may contribute to a better understanding of the biochemical pathogenesis of both vascular dementia and senile dementia of the Alzheimer type.

Subjects and Methods

A total of 28 institutionalized patients in the Department of Geriatrics, University of Tokyo Hospital was selected for the present investigation; in which 14 patients (AD group) (4 males, 10 females) with a mean ± SEM age of 77.6 ± 0.3 years (range 62–89) fulfilled the NINCDS-ADRDA criteria (24) of probable AD, 7 patients (VD group) (4 males, 3 females) with a mean ± SEM age of 74.4 ± 3.1 years (range 56–84) belonged to vascular dementia according to the NINDS-AIREN criteria (25) and the other 7 patients (C group) (4 males, 3 females) with a mean ± SEM age of 78.6 ± 2.4 years (range 67–87) were selected for control subjects without dementia, who had no organic disease affecting the higher cortical functions. AD group was divided into mild AD group (n=7) by the score of HDS, where the score of 10 was taken as a boundary value dividing the two groups.

Lumbar puncture was performed for each patient with informed consent before breakfast and part of the obtained CSF sample was examined for the routine laboratory test including Alb and ACT concentrations and the rest was kept frozen (−80°C) until analysis of the monoaminergic neurochemicals. At the same time a blood sample was obtained for the analysis of serum Alb and ACT concentrations.

The concentrations of albumin in CSF and serum were determined by Latex aggregation method and Brom-Cresol-Green method, respectively. The concentrations of ACT in CSF and serum were also determined by means of the enzyme-linked immunosorbert assay (ELISA) (26). The concentrations of neurochemicals (MHPG, HVA, 5-HIAA) in CSF were determined by the use of a multi-electrode array system (a neurochemical analyzing system, ESA), as described in previous articles (2, 27). The ratio of Alb concentrations in CSF and serum, i.e. Q-Alb, was evaluated as follows:

\[ Q-\text{Alb} = \frac{\text{Alb(CSF)}}{\text{Alb(serum)}} \]

The ratios of ACT in CSF and serum, i.e. Q-ACT, were also evaluated as follows:

\[ Q-\text{ACT} = \frac{\text{ACT(CSF)}}{\text{ACT(serum)}} \]

Intrathecal synthesis of ACT was also calculated by the use of ACT index:

\[ \text{ACT index} = \frac{Q-\text{ACT}}{Q-\text{Alb}} \]

The correlations between Q-Alb and Q-ACT were evaluated for each dementia group and control group. The correlations between Q-Alb and the concentrations of 3 measured neurochemicals were also evaluated for each group. The 2-tailed t-test was used to statistically compare the concentrations of measured substances, Q-Alb, Q-ACT, ACT indices, and correlations between Q-Alb and various factors among the groups.

Results

Serum Alb

No significant differences were observed in the concentrations of serum Alb between AD group (3.61 ± 0.20 g/dl) and control group (3.71 ± 0.06 g/dl). The concentration of serum Alb in AD group (3.7 ± 0.13 g/dl) was significantly lower than those in VT (p<0.05) or C (p<0.001) groups.

CSF Alb

Concentrations of CSF Alb in AD group (34.3 ± 3.2 mg/dl) and VD group (36.7 ± 3.1 mg/dl) were significantly higher than that in C group (27.3 ± 4.4 mg/dl) (p<0.01 and p<0.05, respectively). No significant difference was observed between AD and VD groups.

Q-Alb

Q-Alb in AD (10.2 ± 0.8 × 10⁻³) and VD (10.3 ± 0.8 × 10⁻³) groups were higher than that in C group (7.37 ± 1.21 × 10⁻³) (p<0.001). No significant differences were observed between AD and VD groups.

Serum ACT

Serum ACT in AD (629 ± 77 µg/ml) was higher than those of VD (572 ± 36 µg/ml) and C (560 ± 78 µg/ml) groups. It was significantly higher than that in AD group (p<0.05) but not than C group.

CSF ACT

CSF ACT in AD (6.33 ± 0.73 µg/ml) group was significantly higher than those in VD (5.45 ± 0.75 µg/ml) and C (3.49 ± 0.45 µg/ml) groups (p<0.05 and p<0.001, respectively).

Q-ACT

Q-ACT in AD group (10.62 ± 0.90 × 10⁻³) was significantly higher than those in VD (9.32 ± 0.85 × 10⁻³) and C (6.57 ± 0.77 × 10⁻³) groups (p<0.01 and p<0.001, respectively).

ACT index

ACT index in AD group (1.067 ± 0.059) was significantly (p<0.05) higher than that in VD group (0.938 ± 0.094) but not

510

Internal Medicine Vol. 37, No. 6 (June 1998)
BBB and Q-Alb in Dementia

than that in C (0.988 ± 0.114) group. ACT index in VD group was not significantly lower than that in C group.

**Correlations between Q-Alb and Q-ACT**

Q-Alb and Q-ACT showed a significant positive correlation in AD (r=0.7659, p<0.01) and C (r=0.9060, p<0.01) groups, while not significant in VD (r=0.1943, NS) group, as shown in Table 1. In mild AD group, Q-Alb and Q-ACT showed a significant positive correlation (r=0.9252, p<0.01), while not in severe AD group (r=0.3497, NS). The results of correlations between Q-Alb and Q-ACT are shown in Fig. 1.

**Correlations between Q-Alb and monoaminergic metabolites**

Q-Alb in C group showed a tendency to correlate with MHPG (r²=0.5426, p<0.1) but not with HVA nor 5-HIAA. Q-Alb in VD group showed a tendency to correlate with MHPG (r²=0.2373, p<0.3), HVA (r²=0.3046, p<0.3) and 5-HIAA (r²=0.2852, p<0.3), respectively. Q-Alb in AD group showed a tendency to correlate with HVA (r²=0.1625, p<0.2), but not with MHPG nor 5-HIAA. Q-Alb in mild AD group showed a tendency to correlate with MHPG (r²=0.2095, p<0.4), but not with HVA nor 5-HIAA, while Q-Alb in severe AD group

<table>
<thead>
<tr>
<th>C</th>
<th>VD</th>
<th>AD</th>
<th>Mild AD</th>
<th>Severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>r</td>
</tr>
<tr>
<td>0.9060</td>
<td>0.1943</td>
<td>0.9252</td>
<td>0.3497</td>
<td></td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACT: α₁-antichymotrypsin, AD: Alzheimer type dementia, C: control, VD: vascular dementia.

![Graph](image-url)

**Figure 1. Correlation between Q-Alb and Q-ACT in each group. (A) C, (B) VD, (C) mAD, (D) sAD. Correlation coefficients (r) in C and mAD were high and statistically significant, while those in VD and sAD were low and not significant. ACT: α₁-antichymotrypsin, AD: Alzheimer type dementia, C: control, mAD: mild AD, sAD: severe AD, VD: vascular dementia.**

Internal Medicine Vol. 37, No. 6 (June 1998)
showed a tendency to correlate with HVA ($r^2=0.4984$, $p<0.1$) but not with MHPG nor 5-HIAA. These results of the correlations described above were summarized in Table 2.

## Discussion

For a standard review of BBB, the report by Goldstein and Betz includes the history of investigation about BBB (28). In this study the statistical analysis between Q-Alb, which is a marker of the permeability of BBB, and Q-ACT revealed characteristics of the BBB permeability in demented patients. Q-Alb correlated significantly with Q-ACT with a high correlation coefficient ($r=0.9060$) in C group. In VD group the correlation between Q-Alb and Q-ACT was not significant. In AD group the correlation between Q-Alb and Q-ACT was significant. In mild AD group this correlation coefficient ($r=0.9252$) was especially high, and similar to C group. In severe AD group, however, this correlation coefficient ($r=0.3497$) became statistically not significant, similar to VD group ($r=0.1943$). These similarities among the groups were visualized in Fig. 1. From the obtained results it is suggested that the permeability of BBB in C group is rather well preserved, while it is impaired in VD group and the correlation between Q-Alb and Q-ACT might be indicative of compromised BBB permeability in AD group as a function of the progression of the disease.

The investigation of the correlation between Q-Alb and the concentrations of 3 monoamine metabolites (MHPG, HVA, and 5-HIAA) further clarified the characteristics of the BBB permeability in demented patients, as described above. In C group, Q-Alb showed a tendency to correlate with MHPG, a noradrenergic metabolite, but not with HVA nor 5-HIAA, dopaminergic and serotoninergic metabolites, respectively. This finding may imply that BBB permeability might be regulated by noradrenergic fibers in the normal state.

In VD group Q-Alb correlated with MHPG, HVA and 5-HIAA with nearly the same correlation coefficients although not significant. This finding seems to indicate that the BBB permeability in VD might be regulated not only by noradrenergic but also by dopaminergic and serotoninergic fibers. It was reported that various types of cerebrovascular insults are associated with the elevation of brain serotonin levels and impaired BBB (29), with which the present result might agree.

In AD group Q-Alb showed a tendency to correlate with HVA. In mild AD, Q-Alb showed a tendency to correlate with MHPG similar to the situation in C group. In severe AD group Q-Alb showed a tendency to correlate with HVA similar to the situation in the total AD group. The BBB permeability might be regulated by noradrenergic fibers in the mild stage of AD similar to C group, but it might be changed gradually to be regulated by dopaminergic fibers with the progression of the degenerative disease. The BBB permeability is known to be regulated by central noradrenergic fibers which originate in the locus ceruleus in normal cerebral vessels (30, 31). The present results seem agreeable with these previous reports. In the pathological state the regulation might be changed gradually from noradrenergic to dopaminergic or serotoninergic systems. This consideration would be plausible when considering the pathogenesis of each type of dementia.

In conclusion it was shown that BBB permeability in dementing disorders was compromised according to the etiology of the disease, vascular dementia or Alzheimer type dementia. Further study is necessary to clarify more fully the BBB disorder not only biochemically but also pathologically.

## References


11. Witseniewski HM, Kozlowski PB. Evidence for blood-brain barrier changes

| Table 2. Correlations ($r^2$) between Q-Alb and MHPG, HVA and 5-HIAA in CSF |
|-----------------|--------|--------|--------|--------|--------|
| $r^2$           | C      | VD     | AD     | Mild AD | Severe AD |
| MHPG            | 0.5426 | 0.2373 | (0.0094)| 0.2095 | (0.0719) |
|                 | p<0.1  | p<0.3  |        | p<0.4  |         |
| HVA             | (0.0071)| 0.3046 | 0.1675 | (0.0637)| 0.4984  |
|                 | p<0.2  | p<0.2  | p<0.1  |        |         |
| 5-HIAA          | (0.0228)| 0.2852 | (0.0317)| (0.0407)| (0.0266) |
|                 | p<0.3  |        |        |        |         |

AD: Alzheimer type dementia, C: control, 5-HIAA: 5-hydroxyindole-3-acetic acid, HVA: homovanillic acid, MHPG: 3-methoxy-4-hydroxyphenylglycol, VD: vascular dementia.
BBB and Q-Alb in Dementia


