Effect of Cerebrospinal Fluid Removal on Cerebral Blood Flow and Metabolism in Patients With Alzheimer's Disease Versus Recent Stroke

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SUMMARY Cerebral hemispheric blood flow (HBF) and metabolism were measured before and after withdrawal of 20 to 30 ml of cerebrospinal fluid (CSF) over a 10-minute interval in eight patients with recent cerebral infarction and in four patients with Alzheimer's disease (AD).

Immediately after CSF removal HBF decreased significantly in the AD group (-14%) but showed no significant change in the stroke group (-5%). There was rapid reduction in cerebral venous O2 content and some increase in cerebral venous Pco2 appearing within 60 seconds of CSF withdrawal, interpreted as a rapid reduction of cerebral blood flow (CBF) as judged by cerebral A-VO2 differences. The reduction in CBF was confirmed by the hydrogen clearance method. Reduction of CBF in response to lowering CSF pressure is presumably of neurogenic origin since it was rapid and occurred without changes in Paco2 or MABP. Furthermore, measurement of HBF demonstrated that cerebral metabolism remained constant after CSF removal.

It is postulated that in AD, reduction of HBF following CSF withdrawal is mediated by a disordered neurogenic veno-arterial vasoconstrictive reflex which is stimulated by rapid reduction in CSF pressure (CSFP). In patients with stroke, when cerebral perfusion pressure is increased by lowering CSFP, CBF is maintained constant mostly by a physiological cerebral veno-arterial vasoconstrictive reflex. Apparently, this vasoconstrictive reflex becomes excessive in Alzheimer's disease, possibly due to cerebral neurogenic imbalance.

Introduction

CEREBRAL BLOOD FLOW (CBF) remains constant despite changes in cerebral perfusion pressure, provided the changes in perfusion pressure are not excessive. This phenomenon is known as cerebral autoregulation. Autoregulation occurs in response to changes in perfusion pressure produced by increasing or decreasing arterial blood pressure (termed "blood pressure autoregulation") or, on the other hand, by increasing or decreasing cerebrospinal fluid pressure (CSFP) (termed "CSFP autoregulation"). Change in vasomotor tone of the resistance vessels during blood pressure autoregulation is mediated in part via neurogenic reflex mechanisms and CSFP autoregulation is believed by some to be mediated via pressure effects on the capacitance vessels. It is possible that CSFP autoregulation is also influenced by neurogenic mechanisms.

It has been shown previously that reduction of CSFP by removal of CSF during lumbar puncture in patients with normal pressure hydrocephalus (NPH) resulted in CBF increases. However, there was no CBF change in patients with benign intracranial hypertension after CSF removal. These findings suggested abnormalities in CSFP autoregulatory responses during induced intracranial hypertension in NPH.

The exact role of the cerebral capacitance vessels, which appear to be the primary site for changes in autoregulation after intracranial pressure (ICP) is reduced, remains obscure but possibly is mediated, at least in part, by pressure-sensitive neurogenic reflexes initiated within the walls of the cerebral venous system.

To date, most studies have been concerned with CBF change following increased CSFP which directly and proportionately increases the cerebral venous pressure. It has been proved that under normal physiological conditions, as ICP is raised, CBF is maintained constant unless CSFP exceeds a critical level. Measurements of CBF in patients with increased ICP due to brain tumor showed that CBF was unaffected by increments of ICP up to approximately 450 mm H2O (33 mm Hg). Experimental observations in normal animals showed that CBF did not change during elevation of CSFP up to 60 to 100 mm Hg; thereafter further increases of CSFP led to progressive reduction of CBF.

Despite numerous studies concerned with measurements of CBF during stepwise increases of ICP, the exact mechanisms maintaining autoregulation during intracranial hypertension remain unknown. Recent observations in experimental animals suggest that the cerebral venous system, particularly that portion of the cerebral veins as they enter the dural sinuses, plays an important role in CSFP autoregulation during experimental intracranial hypertension.

The purpose of the present investigation was to measure and compare CBF and metabolism before and after lowering CSFP by removal of 20 to 30 ml of CSF over a 10-minute interval in two groups of patients, one with Alzheimer's disease and the other with recent cerebral infarction. The CSF sample was utilized for biochemical measurements (see Methods).

Clinical Case Material

Cerebral hemispheric blood flow (HBF) and metabolism were measured in eight patients with recent cerebral infarc-
tion and four patients with Alzheimer's disease. Diagnosis of cerebral ischemic infarction was confirmed by clinical examination, four-vessel angiography, radioisotope brain scan, EEG and CSF examination. The diagnosis of Alzheimer's disease was similarly established except for the addition of a neuropsychological test battery which included the Wechsler Intelligence Test, Finger Tapping, Trail Making, Aphasia Testing and the Wechsler Memory Scale.

The patients' age, sex, clinical diagnosis, grade of severity of the neurological deficit, as well as any associated diseases considered to be risk factors for stroke, plus the interval of time between the CBF measurements and the ischemic episode and onset of symptoms of Alzheimer's disease are listed in table 1. Clinical course and severity of the neurological deficit were classified according to a grading system described previously.3

In the group with recent cerebral infarction there were four men and four women ranging in age from 45 to 72 years with a mean age of 55 years. The mean duration between onset of cerebral ischemia and the measurement was 18 days.

In the group with Alzheimer's disease there were two men and two women ranging in age from 73 to 79 years with a mean age of 75 years. The mean duration from the onset of mental deterioration was five to six years. The severity of dementia was graded according to the results of neuropsychological testing.

Procedure for Obtaining Informed Consent

Suitable patients were selected for admission to the study by two or more staff neurologists after reviewing the patients' records and excluding those cases with some medical contraindication to the procedure. Each patient was seen in consultation by a cardiologist and was not admitted to the study if there was cardiological or general medical contraindication to the procedure. Each patient was premedicated with meperidine hydrochloride (50 mg i.m.) and atropine sulfate (0.4 mg i.m.). Local anesthesia was induced at all needle puncture sites of infiltration with 1% procaine hydrochloride. A catheter was inserted under fluoroscopic control via the basilic vein into the ipsilateral cerebral transverse sinus for sampling of cerebral venous blood. A second catheter was placed into the superior vena cava to measure central venous pressure (CVP). A third catheter was inserted into the internal carotid artery ipsilateral to the side of the infarction in order to record arterial blood pressure (BP) and to inject a bolus of hydrogen-saturated saline and radioisotopes for regional cerebral blood flow (rCBF) and volume (rCBV) measurement. Finally, a catheter was inserted into the brachial artery to sample arterial blood.

Lumbar puncture was performed and a catheter was placed in the subarachnoid space in a cephalic direction in order to monitor CSFP and to remove CSF. All pressures were continuously recorded with Statham pressure transducers. The effect of gradual removal of 20 to 30 ml of CSF over an interval of 10 minutes was then examined.

Arterial and cerebral venous oxygen tension (Po2), carbon dioxide tension (Pco2) and pH were recorded by means of electrodes mounted in flow-through cuvettes.16 Oxygen saturation (So2) was monitored by means of reflection oximeters. An infrared absorption CO2 gas analyzer was used to measure arterial and cerebral venous total CO2 content. The first measurement of CBF was made after cerebral A-VO2 differences had remained constant for at least one-half hour. Under these conditions, 20 to 30 ml of lumbar CSF were removed for an interval of 10 minutes.

To measure CBF, a 10-ml bolus of hydrogen-saturated saline was injected into the carotid artery. The clearance curves were recorded from the cerebral venous blood by means of hydrogen electrodes in the cuvettes and calculated by stochastic analysis. To measure rCBF and rCBV a computer-assisted gamma camera was used. The rCBF

Table 1  Case Material

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Interval after onset</th>
<th>Diagnosis</th>
<th>Grade of severity</th>
<th>Associated diseases (risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/M</td>
<td>8 days</td>
<td>R-cerebral infarction</td>
<td>3</td>
<td>Hypertension</td>
</tr>
<tr>
<td>2</td>
<td>51/M</td>
<td>8 days</td>
<td>L-cerebral infarction</td>
<td>3</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>26 days</td>
<td>L-cerebral infarction</td>
<td>3</td>
<td>Hypertension, diabetes</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>11 days</td>
<td>L-cerebral infarction</td>
<td>2</td>
<td>Hypertension, diabetes</td>
</tr>
<tr>
<td>5</td>
<td>50/M</td>
<td>38 days</td>
<td>Brainstem infarction</td>
<td>3</td>
<td>Hypertension, diabetes</td>
</tr>
<tr>
<td>6</td>
<td>40/F</td>
<td>14 days</td>
<td>L-cerebral infarction</td>
<td>3</td>
<td>Hypertension, diabetes</td>
</tr>
<tr>
<td>7</td>
<td>72/F</td>
<td>13 days</td>
<td>L-cerebral infarction</td>
<td>3</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>8</td>
<td>67/F</td>
<td>24 days</td>
<td>Brainstem infarction</td>
<td>2</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Mean</td>
<td>55</td>
<td>18 days</td>
<td></td>
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</table>

Series with Alzheimer's disease

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Interval after onset</th>
<th>Diagnosis</th>
<th>Grade of severity</th>
<th>Associated diseases (risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73/M</td>
<td>4 years</td>
<td>Progressive dementia</td>
<td>Severe</td>
<td>None detected</td>
</tr>
<tr>
<td>2</td>
<td>79/F</td>
<td>10 years</td>
<td>Progressive dementia</td>
<td>Severe</td>
<td>None detected</td>
</tr>
<tr>
<td>3</td>
<td>73/F</td>
<td>6 years</td>
<td>Progressive dementia</td>
<td>Moderate</td>
<td>None detected</td>
</tr>
<tr>
<td>4</td>
<td>76/M</td>
<td>2 years</td>
<td>Progressive dementia</td>
<td>Mild</td>
<td>None detected</td>
</tr>
<tr>
<td>Mean</td>
<td>75</td>
<td>6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. To summarize the effect of withdrawal of CSF on arteriovenous (A-V) difference for oxygen content, CBF (calculated from A-VO2 difference), cerebral venous and arterial PCO2 and MABP in the total series of patients with recent stroke. The parameters were continuously recorded on the polygraph and sampled at intervals. CBF shows a tendency to decrease during withdrawal of CSF; however, this reduction is not statistically significant.

FIGURE 2. To summarize the effect of withdrawal of CSF on cerebral A-V differences for oxygen content, CBF, cerebral venous and arterial PCO2 and MABP in the total number of patients with Alzheimer’s disease. Note the significant increase in A-VO2 difference indicating a rapid and marked reduction of CBF immediately after CSF withdrawal.

Results

Effect of Withdrawal of CSF on CBF

HBF of patients with stroke before and after withdrawal of CSF is shown in table 2 and figure 1. HBF in this group showed no significant change during and after CSF withdrawal. Likewise, mean rCBV showed no change after withdrawal of CSF (table 2). HBF of patients with Alzheimer’s disease before and after CSF withdrawal is shown in table 3 and figures 2 and 3. This group of patients showed a marked and significant reduction in HBF which was significantly greater than that in the group with stroke. Removal of CSF caused an increase in cerebrovascular resistance in both groups (tables 2 and 3).
Table 2: Effect of Withdrawal of CSF on HBF, Metabolism and rCBV in Patients With Stroke

<table>
<thead>
<tr>
<th></th>
<th>Steady state</th>
<th>Immediately after CSF withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBF (ml/100 gm brain/min)</td>
<td>30.4 ± 4.0 (N = 8)</td>
<td>29.1 ± 3.2 (N = 8)</td>
</tr>
<tr>
<td>HMIo2 (ml/100 gm brain/min)</td>
<td>2.64 ± 0.31 (N = 8)</td>
<td>2.67 ± 0.29 (N = 8)</td>
</tr>
<tr>
<td>HMICO2 (ml/100 gm brain/min)</td>
<td>2.63 ± 0.38 (N = 8)</td>
<td>2.62 ± 0.41 (N = 8)</td>
</tr>
<tr>
<td>HRQ (mm Hg/ml/100 gm brain/min)</td>
<td>1.00 ± 0.06 (N = 8)</td>
<td>0.98 ± 0.05 (N = 8)</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/100 gm brain/min)</td>
<td>3.4 ± 0.5 (N = 8)</td>
<td>3.8 ± 0.7* (N = 8)</td>
</tr>
<tr>
<td>rCBV (ml/100 gm brain)</td>
<td>4.0 ± 0.8 (N = 5)</td>
<td>4.3 ± 1.0 (N = 5)</td>
</tr>
</tbody>
</table>

Values = mean ± SD. N = number of cases. *Significant difference compared with steady state values (p < 0.05).

Cerebral Metabolite Effect of Withdrawal of CSF

In the stroke group, after withdrawal of CSF there was no change in HMIo2, HMICO2 and HRQ (table 2). Likewise, in the group with AD, despite reduction of HBF following CSF removal, HMIo2, HMICO2 and HRQ did not show any significant change (table 3). The EEG did not show any significant change during and after withdrawal of CSF in either group.

Effect of Withdrawal of CSF on Hemodynamics and Arterial Blood Gases

Reduction of ICP by removal of CSF did not alter MABP and CVP in either group. Although MABP in the steady state was significantly higher in the stroke group than values measured in the group with AD, CSF removal produced comparable changes in cerebral perfusion pressure. CVP and CSFP were not significantly different between the two groups (table 4).

Likewise, changes in CSFP by withdrawal of 20 to 30 ml of CSF were not different between the two groups. Comparison of the group with stroke to the group with AD showed that the mean age was greater in the group with AD. MABP was significantly greater in the stroke group than in the group with AD, CSFP, although slightly higher in the stroke group, was not significantly different. The pattern of differences can be explained by the cerebral edema associated with stroke and the high incidence of hypertension as a risk factor in patients with stroke. Arterial blood Po2 and Pco2 were not significantly altered by the procedure (table 5).

Table 3: Effect of Withdrawal of CSF on HBF, Metabolism and rCBV in Patients With Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Steady state</th>
<th>Immediately after CSF withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBF (ml/100 gm brain/min)</td>
<td>32.3 ± 1.2 (N = 4)</td>
<td>27.8 ± 2.3* (N = 4)</td>
</tr>
<tr>
<td>HMIo2 (ml/100 gm brain/min)</td>
<td>2.24 ± 0.91 (N = 3)</td>
<td>1.97 ± 0.67 (N = 3)</td>
</tr>
<tr>
<td>HMICO2 (ml/100 gm brain/min)</td>
<td>2.26 ± 0.92 (N = 3)</td>
<td>1.83 ± 0.50 (N = 3)</td>
</tr>
<tr>
<td>HRQ (mm Hg/ml/100 gm brain/min)</td>
<td>1.01 ± 0.05 (N = 3)</td>
<td>0.95 ± 0.10 (N = 3)</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/100 gm brain/min)</td>
<td>2.7 ± 0.4 (N = 4)</td>
<td>3.4 ± 0.6* (N = 4)</td>
</tr>
<tr>
<td>rCBV (ml/100 gm brain)</td>
<td>3.1 (N = 1)</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Values = mean ± SD. N = number of cases. *Significant difference compared with steady state values (p < 0.05).

Discussion

Reduction of CBF immediately after initiating CSF removal in patients with Alzheimer’s disease cannot be attributed to the minimal increase in cerebral perfusion pressure (CPP) where CPP may be regarded as MABP-CSFP, since impaired autoregulation would then increase CBF rather than cause its decrease. It should be mentioned that there is some controversy regarding the best definition of CPP after removal of CSF, although some authors agree that CPP is influenced by changes in CSFP.12 19

Earlier investigations concerning the effects of manipulating the CSFP showed (1) that the pial arteries dilated as CSFP was increased, 20 and (2) that in patients with brain tumor CBF was unaltered until CSFP increased above 33 mm Hg (450 mm H2O).9 Recent experiments showed that CSFP autoregulation remained intact when ICP was increased to a level of 60 mm Hg by inflating a supratentorial balloon. On the other hand, CSFP autoregulation was abolished when ICP was increased by inflating an infratentorial balloon with resulting compression of the brainstem, 21 which suggests that CSFP autoregulation is neuronally mediated via brainstem centers. It should be recognized, however, that other studies have shown that while the autonomic nervous system may modify CBF autoregulation, it is not responsible for the existence of the basic phenomenon.22 There have been few studies made concerning autoregulatory mechanisms when ICP is reduced by removal of CSF. Under normal circumstances CBF remains constant when CSF is removed even in patients with benign intracranial hypertension.23
Let us consider how CSFP autoregulatory mechanisms may function. Since the cerebral venous system has the lowest intramural pressure with the least rigidity of vessel walls, the walls of the cerebral veins may be assumed to be the site most sensitive to changes in CSFP, tissue pressure or ICP, and this may be the site for initiation of the autonomic reflexes responsible for preserving CSFP-CBF autoregulation. For example, the cerebral vasoconstriction that maintains CBF constant after lowering CSFP may be mediated via a "veno-arterial neurogenic reflex." This hypothesis appears to be supported by the following observations. Lowering CSFP to zero in dogs has been reported to reduce CBF accompanied by constriction of the cerebral prevenous segment with dilatation of cerebral veins.28 Postoperative intracranial hypotension in patients with chronic subdural hematoma is often associated with a decrease in CBF due to cerebrovascular constriction.29 In early studies utilizing the skull window technique, it was demonstrated that removal of CSF from the cisterna magna caused dilatation of the cerebral veins and venules and a constriction of the pial arteries with decreased cerebral circulation time.30 Similar venivasomotor reflexes have regularly been observed in many tissues other than the brain including the digits,25 the kidney,31 and the leg.32

There appears to be a general rule throughout all tissues measured, including the brain, that distention of the venous vessel wall, by either decreasing tissue pressure or increasing venous pressure, seems to cause a reflex arteriolar constriction mediated over nervous pathways.37 However, cerebral venous distention by raised ICP or CSFP seems to cause dilatation of the cerebral arteries38 while cerebral venous hypotension brought about by lowered ICP seems to cause vasoconstriction of cerebral arteries.39

From the present study it is apparent that CSFP autoregulation is relatively well preserved in patients with recent cerebral infarction so that after CSF removal, HBF stays relatively constant, while in patients with Alzheimer's disease HBF becomes significantly reduced (−14%). The fact that CVR became significantly increased in both groups can only mean that the decrease in HBF is brought about by cerebral arterial constriction. Since rCBV remained constant as shown in tables 2 and 3, it is likely that blood retention occurred in the capacitance vessels after CSF removal. Since measurements of HBF and metabolism showed no significant change in cerebral oxygen consumption after removal of CSF, continuous measurements of cerebral arteriovenous differences for oxygen content may be utilized for measuring the rapidity of the vascular response and permitted us to measure HBF by the hydrogen bolus technique at the time of the maximum reduction of CBF. This is believed to account for the failure to demonstrate reduction in CBF when the regional flow was measured by intracarotid injection of 133Xe after lowering CSFP by 50% without monitoring cerebral A-VO2 differences.3 There were differences also in the age of the patients and in the severity of the disease in the two studies, which may have influenced the results. Figures 2 and 3 show that there was a rapid reduction of CBF beginning within one minute of removal of CSF and that the reduction of CSFP is unassociated with changes in MABP or Paco2. In one of our patients in whom rCBF measurements were successfully obtained by the 133Xe bolus method immediately before and after CSF removal, the decrease in CBF was diffuse and without significantly different reduction from one region to another.

From perusal of the records, the latent period for development of cerebral vascular constriction following withdrawal of CSF appears to occur within 60 seconds and to appear after withdrawal of less than 5 ml of CSF. The rapidity and sensitivity of this cerebral vasoconstrictive response suggest that it is mediated via a neurogenic reflex mediated from the cerebral venous to the arterial systems. This veno-arterial reflex appears to be responsible for an autoregulatory mechanism from the venous system (cerebral capacitance vessels) to the arterial system (cerebral resistance vessels), which maintain constant CBF during changes in intracranial pressure (cerebral capacitance vessel autoregulation).

As judged from the present study this veno-arterial reflex is excessive in Alzheimer's disease causing a paradoxical hyperconstriction of the resistance vessels or arterioles with reduction of CBF and a dysautoregulation of CSFP-CBF relationships. This abnormal reduction of CBF following

### Table 4: Effect of Withdrawal of CSF on CSF Pressure and Hemodynamics

<table>
<thead>
<tr>
<th>Condition</th>
<th>MABP (mm Hg)</th>
<th>CVP (mm saline)</th>
<th>CSFP (mm saline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>120 ± 14*</td>
<td>74 ± 22</td>
<td>211 ± 102</td>
</tr>
<tr>
<td>E</td>
<td>118 ± 17</td>
<td>77 ± 39</td>
<td>99 ± 87†</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>92 ± 11</td>
<td>53 ± 28</td>
<td>181 ± 47</td>
</tr>
<tr>
<td>disease</td>
<td>91 ± 10</td>
<td>57 ± 21</td>
<td>79 ± 30†</td>
</tr>
</tbody>
</table>

C = Before withdrawal of CSF (steady state); E = after withdrawal of CSF; N = number of cases; values = mean ± SD. *Significant compared to Alzheimer's disease (p < 0.05). †Significant as compared with steady state values (p < 0.05).

### Table 5: Arterial P_{O2} and P_{CO2} Before and After Withdrawal of CSF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Stroke</th>
<th>Alzheimer's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_{O2} (mm Hg)</td>
<td>83.2 ± 10.7 (N = 8)</td>
<td>82.5 ± 5.2 (N = 4)</td>
</tr>
<tr>
<td>P_{CO2} (mm Hg)</td>
<td>41.6 ± 2.4 (N = 7)</td>
<td>38.3 ± 6.5 (N = 4)</td>
</tr>
</tbody>
</table>

C = Before withdrawal of CSF, E = after withdrawal of CSF, N = number of cases, values = mean ± SD.
CSF removal is exactly the opposite to the response seen in patients with normal pressure hydrocephalus, a cause of remediable dementia which may be confused with Alzheimer's disease. It has been shown recently that the dysautoregulation of CBF in relation to CSFP that exists in patients with normal pressure hydrocephalus (capacitance vessel dysautoregulation) results in a significant increase in CBF after CSF removal and is also thought to be due to a neurogenic disorder.

Let us now consider the difference in degree of reduction of HBF between the group of patients with Alzheimer's disease and the group of patients with recent cerebral infarction. In Alzheimer's disease, the autoregulatory response following CSF removal is excessive so that diffuse constriction of the cerebral resistance vessels causes a 14% reduction of overall CBF. This CBF reduction following the removal of a relatively small amount of CSF may be accounted for by either of two possible mechanisms. One mechanism might be denervation hypersensitivity of peripherally located receptors in cerebrovascular walls while the other possible explanation is imbalance of some central monoaminergic neurons causing excessive vessel constriction. The former appears unlikely since it was not observed to occur in patients with stroke where displacement of neurotransmitters into brain tissue and CSF is known to occur. Likewise, peripheral secretion of vasoconstrictive substances from outside of the brain is considered unlikely to occur during CSF withdrawal.

Taking into consideration neurogenic mechanisms, it is well known that most consistent histopathological changes observed in the brains of patients with Alzheimer's disease are frontotemporal atrophy with neuritic plaques and neurofibrillary changes in frontotemporal cortex, and that the maximal reduction of rCBF in Alzheimer's disease is consistently found in the frontal and temporal areas which correlate with the same areas of maximal histopathological change. Recent histochemical studies have shown that in normal brain, the dopaminergic innervation of the frontotemporal cortex is considerably more dense than noradrenergic innervation. There are no data presently available to suggest that any blood vessels in the brain receive a dopaminergic innervation, although this is possible. There is evidence suggesting that cerebral blood vessels in certain areas receive a predominantly noradrenergic innervation. Nevertheless, there is some pharmacologic evidence that in physiologic doses, dopamine may act as a cerebral vasodilator agent. Thus, it may be that in Alzheimer's disease a central monoaminergic system responsible for vasodilatation (such as the cholinergic or, less likely, the dopaminergic systems) may be more impaired than a monoaminergic vasoconstrictor system (such as the noradrenergic or serotonergic systems), whereas in normal pressure hydrocephalus the opposite may be the case.

This imbalance may account for the excessive vasoconstriction following CSF withdrawal observed in the present study. Such a concept of centrally mediated neurogenic imbalance is supported by the work of Gottfries et al. on biochemical assays of the CSF in Alzheimer's disease in which it was shown that dopamine metabolism as reflected by HVA levels in CSF was more clearly affected while the impairment of serotonin metabolism was usually less marked. These observations that HVA and 5-HIAA turnover may be separately depleted in Alzheimer's disease and the neuronal atrophies have been confirmed in our laboratories. On the other hand, severe regional derangement of the monoaminergic system with loss of neurotransmitters from brain tissue into the CSF occurs immediately after onset of stroke and recovers toward the normal state within two to three weeks. These findings correlate with the clinical course of the stroke patients and are in keeping with the remarkable plasticity and regenerative capacity of monoamine neurons after an acute injury. Thus, there appear to be differences in the disorder of monoaminergic systems between patients with Alzheimer's disease and patients with recent cerebral infarction and these may account for the different CSFP autoregulation responses following withdrawal of CSF.

It may be that measurement of CBF before and after withdrawal of CSF may prove to be of diagnostic value since in patients with normal pressure hydrocephalus, reduction of CSFP increases CBF while in patients with Alzheimer's disease CBF decreases, and in patients with recent infarction as a cause of dementia, CBF tends to remain relatively constant. Likewise, in patients with benign intracranial hypertension or brain tumor reduction of ICP by lumbar puncture or ventricular drainage produces no change in CBF. Finally, the cerebral autoregulation test by removal of CSF may provide functional information regarding a state of imbalance of the neurotransmitter systems.

In conclusion, reduction of ICP by withdrawal of CSF decreased HBF significantly in patients with Alzheimer's disease but did not in patients with recent stroke. It is postulated that the veno-arterial reflexes exist in the normal brain, which influence CSFP-CBF autoregulation by stimulating pressure-sensitive receptors in the capacitance vessel walls (cerebral veins). In Alzheimer's disease, CSF removal results in excessive cerebral vasoconstriction which is the opposite response to that seen in normal pressure hydrocephalus. It is postulated that this CSFP dysautoregulation may reflect an imbalance of cerebral neurotransmitter systems.

References


J S Meyer, Y Miyakawa, N Ishihara, Y Itoh, H Naritomi, N T Mathew, K M Welch, V D Deshmukh and A D Ericksson

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