Vasopressin in the cerebrospinal fluid of patients with normal pressure hydrocephalus and benign intracranial hypertension

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Abstract. We have studied plasma and cerebrospinal fluid vasopressin (CSF-AVP) and osmolality in 28 patients with cervical or lumbar pain syndromes (control patients), 11 patients with normal pressure hydrocephalus (NPH) and in 5 patients with benign intracranial hypertension (BIH). Vasopressin concentration in lumbar CSF to a high extent reflected the actual ventricular CSF-AVP concentration. In all groups CSF-AVP was lower than plasma AVP. Mean CSF-AVP in the control group was 1.3 pg/ml ± 0.1 (SEM). In the NPH patients, who all suffered from severe dementia, CSF-AVP level was not different from that found in the control group (1.4 pg/ml ± 0.2). In contrast to the findings in the two other groups CSF osmolality in BIH patients was higher than plasma osmolality (P < 0.02). CSF-AVP in the BIH patients, characterized by an elevated intracranial pressure (ICP), was higher than in the control group (2.7 pg/ml ± 0.4, P < 0.001).

In recent years increasing evidence for the effects of the antidiuretic hormone (8-arginine-vasopres- sin, AVP) on brain function and intracranial pressure (ICP) has been accumulating (Weingartner et al. 1981; Bohus et al. 1978; Raichle & Grubb 1978; Noto et al. 1978).

The first measurements of cerebrospinal fluid AVP (CSF-AVP) were by bioassay techniques (Heller et al. 1968; Vorherr et al. 1968; Gupta 1969). The results were rather inconsistent but demonstrated that CSF-AVP levels were lower than plasma AVP levels. Using a RIA-method Luerssen et al. (1977) found, that CSF-AVP level in humans was rather constant and invariably lower than plasma AVP in patients without endocrine disorders.

Normally CSF samples are obtained by lumbar puncture. In the present study an evaluation was included of the value of lumbar CSF-AVP in the study of the actual brain (i.e. ventricular) CSF-AVP. This was studied in patients with normal pressure hydrocephalus (NPH). Furthermore CSF-AVP level was measured in a group of patients with benign intracranial hypertension (BIH). Patients with cervical or lumbar pain syndromes were studied as a control group without brain disease or pathological CSF hydrodynamics.

Materials and Methods

Patient material

Control patients, patients with lumbar or cervical pain syndrome. The control group comprised 13 females (aged 37–66) and 15 males (aged 28–63), admitted to the department of neurosurgery with symptoms suggestive of a cervical or lumbar disk syndrome. A myelography was performed and no signs of obstruction of the cerebrospinal canal were found in any of the patients. CSF samples were obtained by a lumbar puncture performed under local anaesthesia as part of the diagnostic myelography. CSF pressure was within normal limits in all and none of the patients had symptoms of brain disease or endocrine disorders.
Patients with normal pressure hydrocephalus (NPH). This group comprised 3 females (aged 63–67) and 8 males (aged 39–73). The patients were admitted to the department of neurosurgery because of severe dementia and hydrocephalus. The dementia was confirmed by standard psychological tests, and computerized tomography (CT-scan) revealed central and/or cortical atrophy of the brain (hydrocephalus) in all patients. By a preliminary lumbar puncture it was shown that all patients had normal CSF pressure and composition. None of the patients had signs of endocrine dysfunction.

In all patients a cannula was introduced into a lateral ventricle, with the tip placed near the foramen of Monro. ICP was continuously recorded by a statham 23PM transducer during a 24 h period. At the end of this period a lumbo-ventricular perfusion was performed to study the conductance to CSF-outflow (Børjese et al. 1978). Lumbar and ventricular CSF samples were taken simultaneously before the perfusion study, and the blood samples just before the lumbar puncture. The conductance was severely decreased in all the patients (mean: 0.04 ml/min × mmHg; range 0.09–0.01, normal value > 0.12 ml/min × mmHg) and all the patients have therefore later received a ventriculoatrial shunt (Gjerris et al. 1980).

Patients with benign intracranial hypertension (BIH). This group comprised 2 females aged 38 and 50 years and 3 males aged 13, 32 and 40 years. All patients had headache, enlarged blind spots and papilloedema. Elevated ICP was confirmed in two of the patients by epidural pressure monitoring for 24 h by a transducer (Philips, Eindhoven, Holland) placed through a precoronal burr-hole. ICPs in these two patients were clearly elevated (272 and 408 mmH2O, respectively). In the other patients ICPs were measured by lumbar puncture in the recumbent position under local anaesthesia. The pressures were 250, 240 and 390 mmH2O, respectively.

In all patients CSF protein was normal (mean: 0.35 g/l; range 0.25–0.45). An intracranial tumour was excluded and the diagnosis of BIH was confirmed by a CT-scan (Delaney & Schellinger 1976). CSF samples were obtained by lumbar puncture and blood samples taken just before the lumbar puncture.

Analytical methods
Vasopressin. AVP concentrations were measured by a radioimmunoassay (Hammer 1978). Both plasma and CSF samples were extracted with acetone and petroleum ether as previously described. All values were corrected for the actual loss during the extraction procedure. The sensitivity of the analysis was 0.5 pg/ml when 2 ml samples were extracted. The intra- and inter-assay coefficients of variation were 5–10% and 15%, respectively. Cross-reactions with oxytocin and vasotocin, two hormones which are chemically closely related to AVP and known to appear in CSF, were less than 1×10⁻⁵. By gel filtration of the extracted samples on a Sephadex DEAE-25 column (1 × 60 cm) it was secured that the immunoreactive material was recovered in the same fractions as the synthetic AVP standard (Ferring, Sweden), which had a biological potency of 400 IU/mg.

Osmolality. Plasma and CSF osmolalities were measured by freezing point depression (Knauer automated osmometer). The coefficient of variation was less than 1%.

Statistical methods. Test for differences in hormone or osmolality levels were made by one- or two-way analysis of variance.

Results
Control patients
Plasma and CSF osmolalities were not significantly different (Table 1). AVP concentration was significantly lower in CSF than in plasma (P < 0.001) and the two variables were weakly correlated (P < 0.05, Fig 1). The equation for the regression line was: Y = 0.17 X + 0.71.

In 22 of the patients 15 ml CSF was tapped in 3

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<th>Vasopressin conc (pg/ml)</th>
<th>Osmolality (mOsm/kg H2O)</th>
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<tr>
<td></td>
<td>plasma</td>
<td>CSF</td>
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<tr>
<td>Control patients</td>
<td>n = 28</td>
<td>3.6 ± 0.2</td>
</tr>
<tr>
<td>NPH patients</td>
<td>n = 11</td>
<td>3.0 ± 0.6</td>
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<tr>
<td>BIH patients</td>
<td>n = 5</td>
<td>4.6 ± 1.0</td>
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* (P < 0.05) compared with plasma value. ** (P < 0.05) compared with CSF value in the control patients.
fractions, 5 ml each. The mean AVP concentrations (±SEM) in the three samples were: 0–5 ml: 1.3 pg/ml ± 0.1; 5–10 ml: 1.4 pg/ml ± 0.1; 10–15 ml: 1.4 pg/ml ± 0.1.

Patients with normal pressure hydrocephalus
Neither plasma nor CSF osmolalities of the 11 patients differed from those found in the control group (Table 1), and CSF-AVP level in samples obtained from the lumbar site was equal to the level in the control group.

CSF-AVP in simultaneously obtained samples from the lateral ventricles in 7 of the patients were slightly higher than in the samples from the lumbar site (Fig. 2). The differences were, however, very small, indicating a reasonable reliability of the measurements of AVP in lumbar CSF.

Patients with benign intracranial hypertension
AVP plasma and osmolalities of the 5 patients were not different from those found in the control patients (Table 1). However, in contrast to the control patients, CSF osmolalities were higher than plasma osmolalities in all patients. Furthermore, the mean CSF osmolality was higher than in the control group ($P < 0.02$).

Mean CSF-AVP was lower than mean plasma
AVP in all three groups of patients. But the differences in the BIH patients were small, and in one patient with BIH, CSF-AVP was higher than plasma AVP. Mean CSF-AVP was higher in BIH patients than in the control group (Table 1, Fig. 3). The 2 patients who had the highest CSF-AVP's had the highest ICP values too. However, the relationship between ICP and CSF-AVP in the 5 patients was not significant \(r = 0.86; 0.10 > P > 0.05\).

Discussion

The origin of vasopressin in CSF remains unclear. By immunohistochemical methods vasopressinergic nerve endings have been demonstrated in several regions of the brain, brain stem and spinal cord (Weindl & Sofroniew 1980). The way AVP is cleared from these nerve endings is not known. It has been suggested, that clearance takes place by simple diffusion of AVP into the CSF. The distribution of neurons containing AVP indicates, that most of the AVP in CSF is secreted by cells and nerve endings in the brain and transported by the usual flow of CSF to the lumbar cistern.

In the present study we have found that the AVP level in CSF samples obtained by lumbar puncture to a high extent reflected the actual AVP level in ventricular CSF (Fig. 2). Our results also showed, that the AVP concentration in lumbar CSF did not change within the first three fractions of 5 ml each.

The results of the present investigation were in accordance with previous studies, showing that CSF-AVP was lower than plasma AVP (Vorherr et al. 1968; Heller et al. 1968; Gupta 1969; Luerssen et al. 1977). The level of CSF-AVP found in our control group (Table 1) was identical to that found by Luerssen et al. (1977) also by a RIA-method. The results of two recent reports have, however, been controversial. Dogterom et al. (1978) reported high levels of AVP in CSF, while in plasma AVP was undetectable in 5 of 10 patients. Jenkins et al. (1980) found, that the CSF-AVP level in patients without intracranial diseases was nearly the same as plasma AVP level. The reason for the discrepancy between these and earlier studies remains unclear. One explanation might be that the samples in some cases were obtained under anaesthesia, another that non-hormonal factors interfered in the assay procedure. For a discussion see Luerssen & Robertson (1980).

In the present study the equation of the regression line describing the relationship between plasma and CSF-AVP was nearly identical to the equation found by Luerssen & Robertson (1980). Vorherr et al. (1968) observed, that severe bleeding of the animals caused an increase of both plasma and CSF-antidiuretic hormone activity. A direct overflow of AVP from plasma to CSF has been excluded (Vorherr et al. 1968; Zaidi & Heller 1974; Luerssen et al. 1977). Thus, the relationship between plasma and CSF-AVP and the results obtained by bleeding indicate, that secretion of AVP into the blood stream and into the CSF have at least some determinant stimuli in common.

AVP may affect memory processes in humans (Weingartner et al. 1981). The CSF-AVP level, in our patients with NPH, who all demonstrated severe defects in learning and memory processes, was not different from the CSF-AVP level in the control group. An effect of AVP on memory function in these patients is, however, not excluded by the present results, as these patients might have had damages in the anatomical substrate for AVP.

The pathophysiology of benign intracranial
hypertension remains obscure. Although a defect of CSF absorption has been reported by several groups (Johnston 1973; Sklar et al. 1979; Janny et al. 1981) this cannot be the only pathophysiological determinant of BIH. For a discussion see Sklar et al. (1979).

It might be proposed, that the elevated CSF-AVP and osmolality levels in BIH patients are caused simply by a concentrating effect of the decreased CSF absorption. However, the CSF absorption capacities in our NPH patients, all having normal CSF-AVP and osmolality, were only half of that reported for BIH patients. Secondly, the concentrating effect would have had to be selective as the total protein concentration of the CSF was normal in all BIH patients. We must therefore conclude, that the elevated CSF-AVP in this clinical condition is due to an increased secretion of AVP into the CSF.

Recent results obtained in rabbits and monkeys indicate that AVP in CSF increases CSF water efflux and thereby decreases intracranial pressure (Raichle & Grubb 1978; Noto et al. 1978). Consequently, the increased CSF to plasma osmolality ratio in the BIH patients might be explained by the increased CSF-AVP level in these patients. However, the reason for the elevated AVP level in CSF in these patients is not explained by any known mechanism.

We propose as a hypothesis, that increased intracranial pressure, as found in BIH, causes an increased secretion of AVP into the CSF, which would tend to reduce the intracranial pressure.

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References


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