Cerebrospinal fluid vasopressin in neurological and psychiatric disorders

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SUMMARY Vasopressin was determined in CSF and plasma of 243 patients with different neurological and psychiatric disorders, including control patients. CSF vasopressin was significantly higher in patients with high pressure hydrocephalus, intracranial tumour, benign intracranial hypertension, intracranial haemorrhage, ischaemic stroke, and craniocerebral trauma. In patients with primary degenerative dementia, CSF vasopressin was lower than in control patients. Among patients with psychiatric disorders, CSF vasopressin was increased in manic patients, while in patients with depression CSF concentration of this hormone did not differ from that found in controls. However, an increase in CSF vasopressin level was found in patients recovering from a depression. The clinical significance of changes in CSF vasopressin concentrations in groups of patients with neurological and psychiatric disorders is still unknown.

The neurohypophyseal hormone arginine vasopressin (AVP) has been demonstrated in various extrahypothalamic locations within the central nervous system¹⁻⁵ and AVP is found in the cerebrospinal fluid (CSF) of normally hydrated subjects in concentrations similar to or lower than the corresponding plasma concentrations.⁶⁻⁸ However, in a number of neurological disorders a diverging ratio of CSF/plasma concentration has been found indicating a separate regulation of the release of AVP into the CSF.⁹⁻¹¹

Several hypotheses on the function of AVP within the central nervous system have been offered. Vasopressin in the CSF has been suggested to have an effect on brain water permeability¹² and on the intracranial pressure,¹³ and a direct relationship between the intracranial pressure and CSF AVP concentration has been proposed.¹¹ Several results from animal studies have suggested that AVP might influence learning and memory functions, and low CSF concentrations of AVP have been found in patients with dementia.^{16,17} Gold *et al.* have proposed the hypothesis that AVP is implicated in changes of mood in manic-depressive illness.¹⁸

In the present study AVP concentrations in CSF

and plasma have been measured in an extended number of patients with dementia and intracranial hypertension, and we have included several other groups of patients with neurological and psychiatric disorders and control patients with no signs of central nervous system disease.

Materials and methods

Control patients

This group comprised 52 patients, 22 men and 30 women, aged 21-76 years, median age 46 years (table 1). Twenty-eight patients had symptoms of a cervical or lumbar disc syndrome and were admitted for diagnostic myelography. Eleven patients had headache or common migraine. Seven patients had diffuse neurological symptoms as dizziness or paraesthesia, but no signs of organic disease were found. Six patients had minor peripheral neurological symptoms. No patients had signs indicating central nervous system lesions and no endocrine disorders were suspected. No medication was given at the time of examination. CSF and blood samples were taken between 8 and 11 am in connection with the myelography in patients with disc syndromes and at a diagnostic lumbar puncture in the other patients. All patients were fasting overnight and were kept supine for 30 min before the lumbar puncture which was performed using local anaesthesia and with the patients in the lateral recumbent position. The CSF pressure was measured before removal of CSF. All patients had normal CSF pressure, protein concentration, and cell count. Venous blood samples were obtained just before the lumbar puncture. Informed consent was obtained from all patients.

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Table 1 Age and sex distribution in groups of patients with neurological and psychiatric disorders and controls.

Diagnosis	N	Age (yr) Median	Range	Sex Male	Female
Normal pressure hydrocephalus	29	65	37-72	19	10
High pressure hydrocephalus	6	29	2-62	2	4
Intracranial tumour	14	47	7-73	9	5
Benign intracranial hypertension	18	35	13-53	4	14
Intracranial haemorrhage	9	52	28-66	2	7
Ischaemic stroke	10	61	42-70	7	3
Cranio-cerebral trauma	5	52	12-60	3	2
Multiple sclerosis	8	39	15-59	5	3
Basal ganglia disorders	5	42	20-63	2	3
Primary degenerative dementia	25	56	30-71	19	6
Endogenous depression	32	46	18-82	16	16
Non-endogenous depression	14	47	22-66	6	8
Mania	7	34	30-49	1	6
Schizophrenia	9	29	19-40	6	3
Controls	52	46	21-76	22	30

Patients with diseases of the central nervous system

All patients with neurological disorders were admitted to the Neurological og Neurosurgical Clinics, Rigshospitalet. Age and sex distribution in the different patient groups is given in table 1. None of the patients received any medication and none had clinical signs of endocrine diseases. CSF and blood samples were taken using the same procedure as in the control patients. However, in two patients with high pressure hydrocephalus, in all patients with intracranial tumour or cranio-cerebral trauma, and in seven patients with intracranial haemorrhage ventricular CSF specimens were obtained due to the hazards of lumbar puncture in these patients.

Normal pressure hydrocephalus. Twenty nine patients had clinical symptoms of normal pressure hydrocephalus: dementia, gait disturbances, and/or urinary incontinence. All had ventricular enlargement in CT-scan, some with periventricular lucency. The intraventricular pressure was normal (<12 mm Hg), and all had decreased conductance to CSF-outflow measured by a lumbar-ventricular perfusion study.¹⁹ In 17 patients lumbar and ventricular CSF samples were taken simultaneously in connection with the perfusion study.

High pressure hydrocephalus. Six patients had high pressure hydrocephalus: two had communicating high pressure hydrocephalus as a complication to subarachnoid haemorrhage, one as a complication to an ependymoma of the cauda equina, and one was suspected to have congenital stenosis of the aqueduct of Sylvius. The last two patients were children with congenital hydrocephalus and obstruction of a previously placed ventriculo-atrial shunt. In all patients the intraventricular pressure was increased (≥ 18 mm Hg).

Intracranial tumour. Fourteen patients had intracranial tumours, including five acoustic neuromas, two cerebellar astrocytomas, one cerebellar haemangioblastoma, one fourth ventricle papilloma of the choroid plexus, two pinealomas, two cerebral gliomas, and one craniopharyngeoma. Seven of the patients had complicating obstructive hydrocephalus. Eleven patients had increased intraventricular pressure (≥ 18 mm Hg).

Benign intracranial hypertension. This group comprised 18

patients fulfilling the following diagnostic criteria: raised intracranial pressure, papilloedema, normal or diminished ventricular size on CT. The intracranial pressure, measured by epidural pressure monitoring in 12 patients, and via a lumbar cannula in six patients, was increased (≥ 18 mm Hg) in 13 of the 18 patients. All had low or normal CSF protein concentration.

Intracranial haemorrhage. This group comprised nine patients with either recent subarachnoid haemorrhage (six patients) or intracerebral haematoma (three patients). The intracranial pressure was measured by intraventricular pressure monitoring in seven patients and by lumbar puncture in two. Six patients had increased (≥ 18 mm Hg) intracranial pressure.

Ischaemic stroke. Ten patients were examined during the week following an ischaemic stroke. The diagnosis was confirmed by CT which showed a lesion compatible with a cerebral infarct. The intracranial pressure was elevated (≥ 18 mm Hg) in two patients. None of the patients had haemorrhagic CSF.

Cranio-cerebral trauma. This group comprised five patients, of whom three had cerebral contusion, one traumatic subarachnoid haemorrhage, and one epidural haematoma. The intraventricular pressure was increased (≥ 18 mm Hg) in three patients.

Multiple sclerosis. Eight patients had multiple sclerosis diagnosed according to the criteria of Schumacher *et al.*²⁰ and the diagnosis was confirmed by abnormalities in visual or somatosensory evoked potentials and/or signs of intrathecal IgG production. The lumbar CSF pressure was normal.

Miscellaneous basal ganglia disorders. The group comprised five patients, of whom two had Parkinson's disease, one Huntington's chorea, one torsion dystonia, and one Gilles de la Tourette syndrome. Normal lumbar CSF pressure was found in all patients.

Primary degenerative dementia. Twenty five patients with a history of progressive dementia were studied. The diagnosis primary degenerative dementia was made by history, neuropsychological examination, metabolic screening, and CT. None of the patients had symptoms of multi infarct dementia. All had normal CSF pressure measured by lum-

bar puncture.

Patients with psychiatric disorders

The psychiatric patients were all admitted to the Department of Psychiatry, Rigshospitalet. All diagnoses and ratings were made by a psychiatrist who did not otherwise take part in the study. None of the patients had any known endocrine disease. In all groups of psychiatric patients, measurement of lumbar CSF pressure, collection of CSF and blood samples were performed following the same procedures as described in the control patients. Age and sex distribution in the different patient groups is shown in table 1.

Endogenous depression (melancholia). Thirty two patients were classified as endogenous depression according to the International Classification of Diseases, 8th Edition (ICD-8) (296). The patients were rated using the Bech-Rafaelsen melancholia scale (BRMES)²¹ and all patients entering the study had a score above 15. None of the patients received any medication at the time of study except one patient who was treated with lithium carbonate. Twelve patients were reexamined after they had recovered from the depression, represented by a score below 7 in the BRMES. Two patients had been treated with electroconvulsive therapy, eight with antidepressant drugs, one with antidepressant drugs and lithium carbonate, and one with lithium carbonate alone.

Non-endogenous depression. This group consisted of 14 patients, including the ICD-8 diagnoses 298 (reactive depression), 299 (other psychotic depression), 300 (depressive neurosis), and 301 (cyclothymic personality). None of the patients received any medication.

Mania. Seven patients with manic-depressive psychosis (ICD-8: 296) were examined in a manic phase, all having a score above 10 on the Bech-Rafaelsen mania scale (BRMS).²² All were without any medication when studied.

Schizophrenia. Nine patients diagnosed as schizophrenic according to ICD-8 (295) were included. This group comprised both acute and chronic schizophrenic patients. At the time of examination none of the patients received any medication.

Analytical methods

CSF and blood for AVP analyses were sampled in chilled tubes and placed on ice. The blood samples were taken in plastic tubes containing 8 mg Na₂-EDTA and separated immediately. Blood for osmolality measurements was collected in heparinised tubes. Plasma and CSF samples were stored at -20°C until analyses. CSF and plasma AVP concentrations were determined by radioimmunoassay after extraction of 2 ml samples in duplicate with acetone and petroleum ether as previously described.²³ The sensitivity of the analysis was 0.5 pg/ml and the intra- and inter-assay coefficient of variation were 5-10% and 15%, respectively. In studies using gelfiltration of the extracted CSF and plasma samples, the immunoreactivity was recovered in the same fraction as the synthetic AVP standard (Ferring, Sweden). Plasma and CSF osmolality were determined by freezing point depression (Knauer automated digital osmometer), coefficient of variation was less than 1%.

Statistical analyses were performed using analysis of variance and Student's *t* test for paired data. As hormone values in some of the patient groups could not be assumed to be normally distributed, Kruskal-Wallis test was employed. Significance levels: $\alpha = 0.05$, 0.01 and 0.001.

Results

Control patients

CSF and plasma AVP concentration and osmolality are shown in table 2 and 3 and fig. Mean CSF AVP concentration was 1.3 ± 0.1 pg/ml (SEM), and no difference was found between men (1.4 ± 0.1 pg/ml (SEM)) and women (1.3 ± 0.1 pg/ml (SEM)). No statistical correlation was found between age and CSF AVP concentration ($r = -0.01$). Plasma AVP was higher than CSF AVP in all patients but three, but no statistical correlation was found between plasma and CSF vasopressin concentrations ($r = 0.22$; $p > 0.1$). Plasma and CSF osmolalities were

Table 2 Vasopressin concentration and osmolality in CSF and plasma in groups of patients with different neurological disorders and in controls (Means $\pm$ SEM).

Diagnosis	N	Vasopressin conc. (pg/ml)		Osmolality (mosm/kg H ₂ O)	
		CSF	Plasma	CSF	Plasma
Normal pressure hydrocephalus	29	1.3 ± 0.1	3.5 ± 0.4	283 ± 1	284 ± 1
High pressure hydrocephalus	6	$2.4 \pm 0.5\ddagger$	2.9 ± 0.8	281 ± 4	279 ± 4
Intracranial tumour	14	$2.5 \pm 0.3\ddagger$	$4.9 \pm 1.1\ddagger$	287 ± 3	285 ± 2
Benign intracranial hypertension	18	$1.9 \pm 0.2\ddagger$	2.8 ± 0.4	285 ± 2	284 ± 2
Intracranial haemorrhage	9	$1.9 \pm 0.3^*$	$5.0 \pm 1.1\ddagger$	274 ± 10	280 ± 8
Ischaemic stroke	10	$1.8 \pm 0.3^*$	2.7 ± 0.8	$291 \pm 4^*$	288 ± 2
Cranio-cerebral trauma	5	$2.0 \pm 0.3\ddagger$	3.4 ± 1.0	$272 \pm 12\ddagger$	$269 \pm 10\ddagger$
Multiple sclerosis	8	1.5 ± 0.1	3.0 ± 0.4	284 ± 3	285 ± 3
Basal ganglia disorders	5	1.3 ± 0.2	$2.0 \pm 0.3^*$	283 ± 3	284 ± 2
Primary degenerative dementia	25	$0.9 \pm 0.1\ddagger$	$1.8 \pm 0.2\ddagger\ddagger$	284 ± 1	286 ± 1
Controls	52	1.3 ± 0.1	3.1 ± 0.2	283 ± 1	286 ± 1

* $p < 0.05$ compared with controls.

$\ddagger p < 0.01$ compared with controls.

$\ddagger\ddagger p < 0.001$ compared with controls.

Table 3 Vasopressin concentration and osmolality in CSF and plasma in groups of patients with different psychiatric disorders and in controls (Means $\pm$ SEM).

Diagnosis	N	Vasopressin conc. (pg/ml)		Osmolality (mosm/kg H ₂ O)	
		CSF	Plasma	CSF	Plasma
Endogenous depression	32	1.3 $\pm$ 0.1	2.6 $\pm$ 0.3	284 $\pm$ 1	288 $\pm$ 1
Non-endogenous depression	14	1.2 $\pm$ 0.1	2.4 $\pm$ 0.3	284 $\pm$ 2	288 $\pm$ 2
Mania	7	1.9 $\pm$ 0.3*	2.6 $\pm$ 0.5	282 $\pm$ 1	286 $\pm$ 3
Schizophrenia	9	1.5 $\pm$ 0.1	2.6 $\pm$ 0.4	283 $\pm$ 2	287 $\pm$ 2
Controls	52	1.3 $\pm$ 0.1	3.1 $\pm$ 0.2	283 $\pm$ 1	286 $\pm$ 1

* p < 0.01 compared with controls.

not significantly different, and a significant correlation was found between plasma osmolality and plasma AVP concentration ($r = 0.46$; $p < 0.001$).

Patients with diseases of the central nervous system

CSF and plasma AVP concentrations and osmolalities are shown in table 2 and fig. Mean CSF AVP concentration was higher in patients with high pressure hydrocephalus, intracranial tumour, benign intracranial hypertension, intracranial haemorrhage, ischaemic stroke, and cranio-cerebral trauma, that is in all groups of patients where raised intracranial pressure frequently was observed. In patients with multiple sclerosis and basal ganglia disorders mean CSF AVP was not different from the value found in the control patients. However, low values of CSF AVP were found in two patients with Parkinson's disease (0.8 and 1.0 pg/ml). Patients with primary degenerative dementia had significantly reduced CSF AVP concentration (0.9 $\pm$ 0.1 pg/ml (SEM)) compared with controls. No significant difference was found between simultaneously sampled lumbar (1.4 $\pm$ 0.1 pg/ml (SEM)) and ventricular (1.5 $\pm$ 0.1 pg/ml (SEM)) CSF from 17 patients with normal pressure hydrocephalus.

Mean plasma AVP concentration was increased in patients with intracranial tumour and intracranial haemorrhage and decreased in patients with basal ganglia disorder and primary degenerative dementia when compared with mean plasma AVP in the control patients. No relationship was found between CSF and plasma AVP values in any of the patient groups, except in patients with benign intracranial hypertension ($r = 0.65$; $p < 0.01$).

Mean plasma and CSF osmolalities did not differ from the values found in controls except in the group of patients with cranio-cerebral trauma. Two patients with cranial trauma, two with intracranial tumour and one with subarachnoid haemorrhage had symptoms of inappropriate secretion of anti-diuretic hormone syndrome with severe hyposmolality (<260 mosm/kg) and hyponatraemia and normal or even high plasma AVP concentrations. The relationship between plasma osmolality and plasma

AVP, which was demonstrated in the control patients, was not present in any group of patients with intracranial disorders, and several patients showed plasma AVP concentrations which in relation to the corresponding plasma osmolalities were outside the range found in normal subjects.²⁴

Patients with psychiatric disorders

CSF and plasma AVP concentrations and osmolalities are given in table 3 and fig. Mean CSF AVP concentration was higher in manic patients while depressive and schizophrenic patients had values similar to that found in control patients. However, in 12 endogenous depressive patients who were examined during depression and reexamined after recovery, CSF AVP was lower in the state of depression (1.2 $\pm$ 0.1 pg/ml (SEM)) than after recovery (1.5 $\pm$ 0.1 pg/ml (SEM); $p < 0.05$).

Mean plasma AVP was not different from that found in control patients in any group of psychiatric patients. In patients with endogenous depression and in patients with mania plasma AVP and CSF AVP concentrations were significantly correlated ($r = 0.47$ and $r = 0.82$, respectively; $p < 0.01$), whereas such a correlation was not seen in the control patients.

Plasma and CSF osmolalities were within the normal range (table 3), but a relationship between plasma osmolality and plasma AVP, as found in the controls, could not be demonstrated in any group of psychiatric patients.

Discussion

The concentration of AVP in CSF was increased in those intracranial disorders that commonly cause raised intracranial pressure. This is consistent with previous findings of a direct relationship between the intracranial pressure and CSF AVP concentration in a smaller series of patients with intracranial hypertension.¹¹ Some of the neurological conditions are characterised by damage of brain tissue and possible breakdown of the blood-CSF barrier, which could contribute to the raised CSF AVP concentra-

Fig Cerebrospinal fluid vasopressin in patients with different neurological diseases (upper panel) and in patients with different psychiatric disorders and control patients (lower panel). The area between solid lines indicates the 95% confidence interval for controls. (NPH: normal pressure hydrocephalus; HPH: high pressure hydrocephalus; IC: intracranial; BIH: benign intracranial hypertension; MS: multiple sclerosis; basal ganglia: Miscellaneous basal ganglia disorders; PDD: primary degenerative dementia; Endogen.: endogenous)

tion. However, high CSF AVP concentrations were also found in patients with benign intracranial pressure with no signs of abnormal blood-CSF barrier function. Hence, the raised intracranial pressure probably is a contributory cause of the increase in CSF AVP. In patients with multiple sclerosis and basal ganglia disorders, in whom a normal intracranial pressure was measured, no changes in CSF AVP were found. Our findings are in accordance with previous observations of increased CSF AVP in sporadic cases of intracranial tumor,⁷ subarachnoid haemorrhage,⁹ meningitis,²⁵ and cerebrovascular disease.¹⁷ Sørensen *et al*¹⁰ found CSF AVP increased in patients with benign intracranial hypertension when compared with controls, and the same observation was made by Reid and Morton²⁶ who, however, found CSF AVP equally increased in other neurological patients with normal intracranial pressure. The increased AVP concentrations in CSF, found in various neurological disorders with raised intracranial pressure, is unlikely to be the cause of the intracranial hypertension. However, animal experiments have implicated CSF AVP in brain water permeability¹² and brain water accumulation,²⁷ and if inference can be made from these studies it is possible that increased concentrations of AVP in the CSF might be an additional harmful factor in patients with increased intracranial pressure. It might be argued that comparison of AVP concentrations in ventricular and lumbar CSF is involved. In the present study simultaneously sampled CSF from the ventricular system and the lumbar cistern in the patients with normal pressure hydrocephalus did not disclose any rostro-caudal gradient for the hormone. However, a certain caution must be exercised when comparing AVP concentrations in CSF obtained from different levels within the neuroaxis in these patients with abnormal CSF dynamics. In a previous study⁸ we found no changes in the AVP concentration in three consecutive 5 ml fractions of CSF drained from the lumbar cistern of control patients with assumed normal CSF dynamics.

The present study has confirmed previous findings of decreased CSF AVP in patients with organic dementia.^{16,17} A single study, however, reported increased CSF AVP levels in senile dementia, but was unable to detect AVP in CSF of control patients.²⁸ Low levels of AVP in CSF was found in a small number of patients with dementia caused by alcoholism.²⁹ The findings of low CSF AVP levels in dementia would be consistent with findings of low AVP contents in brains of demented patients. Rosor *et al*,³⁰ however, found only insignificantly decreased AVP content in brains of patients with Alzheimer dementia, whereas Mann *et al*³¹ found

signs of reduced protein synthetic capacity in cells of the supraoptic and paraventricular nuclei in patients with Alzheimer disease. It should be emphasised, however, that a certain caution must be exercised in drawing conclusions regarding the implication of AVP in memory processes from findings of low AVP concentrations in CSF. Other neuropeptides³² and enzyme systems³⁰ have been found reduced in Alzheimer disease, and the reduction of neuropeptides including AVP might only be an epiphenomenon to the diffuse loss of cells within the central nervous system. A number of therapeutic trials have been conducted using intranasally administered AVP and synthetic analogues for treatment of memory disturbances of various kind.³³⁻³⁹ The results of these trials have been conflicting, but regarding the controlled studies mainly negative. The inability of AVP and synthetic analogues to pass the blood-CSF barrier^{40,41} might be the main cause for the negative results in trials using intranasally drug administration.

In the present study, the AVP concentration in CSF of endogenously depressed patients was not different from that found in controls, whereas CSF AVP was increased in manic patients. Thus, the result of the present study is not inconsistent with the findings of Gold *et al*^{42,43} that CSF AVP is decreased in the depressed state of affective illness and increased in mania, as we observed an increase in CSF AVP concentration in patients who recovered from a depression. In a previous study we have shown that treatment of depressed patients with electroconvulsive therapy evokes a marked but transient increase in plasma AVP concentration, and a trend toward a moderate rise in basal plasma AVP levels was found in patients who responded satisfactorily to electroconvulsive therapy.⁴⁴

The present study has demonstrated that significant alterations in CSF AVP levels can be found in various neurological and psychiatric diseases. However, the clinical significance of changes in CSF AVP levels is still obscure and further studies are needed on this subject.

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