CSF and plasma vasopressin concentrations in dementia

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SUMMARY In 16 patients with primary degenerative dementia mean CSF vasopressin concentration was lower (0.9 ± 0.1 pg/ml (mean $\pm$ SEM)) than in 28 control patients (1.3 ± 0.1 (mean $\pm$ SEM)) ($p < 0.01$). In 18 patients with normal pressure hydrocephalus and potentially reversible dementia mean CSF vasopressin concentration (1.2 pg/ml ± 0.1 (mean $\pm$ SEM)) was not different from that found in controls. Several of the demented patients had inappropriate plasma vasopressin concentrations suggesting a defect in osmoregulation. These findings encourage further clinical trials of vasopressin in patients with primary degenerative dementia, but it is emphasised that the low CSF vasopressin concentration in these patients might be only a nonspecific phenomenon due to the diffuse loss of cells within the central nervous system.

Vasopressin (AVP) is a neurohypophysial hormone, which is found in the CSF of normal human subjects in concentrations usually lower than those found in plasma. The blood-brain barrier is impermeable to AVP.¹ Vasopressinergic nerve endings have been demonstrated outside the hypothalamus in several locations in the central nervous system. However, the functional significance of these systems and CSF AVP has not been fully elucidated.²⁻⁴ Assuming that AVP within the central nervous system has separate origin and functions, the CSF AVP concentration would probably indicate the current level of activity of the vasopressinergic systems projecting inside the central nervous system. AVP has been implicated in memory processes in animals,^{5,6} and these findings have encouraged the use of AVP and synthetic analogs in a number of clinical trials in patients with various memory defects.⁷⁻⁹ Measurements of CSF AVP concentrations in patients with impaired cognitive functions would be of interest in order to study possible signs of abnormal AVP release inside the central nervous system.

We have studied CSF and plasma AVP concen-

trations in two groups of patients characterised by presenile dementia, that is, patients with primary degenerative dementia showing a progressive development of cognitive dysfunction, and patients with a potentially reversible dementia connected with normal pressure hydrocephalus.

Patients and methods

The patients with presenile dementia comprised two groups: patients with primary degenerative dementia and patients with dementia connected with normal pressure hydrocephalus. The degree of intellectual impairment was assessed by a number of standard psychometric tests including the WAIS, and the dementia was graded as moderate or severe. Tests for aphasia and related cerebral dysfunctions were also carried out. The presence of central, cortical or focal cerebral atrophy was determined by computed tomography (CT).

Sixteen consecutive patients with the presumptive diagnosis of primary degenerative dementia were studied (10 men and 6 women, ages 30 to 63 years, median age 54 years). The youngest patient in this group was a woman of 30 with strong family history of presenile dementia. Her mother, two maternal uncles, and her grandmother had all died with presenile dementia before the age of 50. The history of cognitive dysfunction varied from a few months to 3 years. The degree of intellectual impairment and cerebral atrophy in CT is shown in table 1. All patients were investigated for metabolic, infectious and toxic disorders known to cause cognitive impairment, but no underlying cause of dementia was found in any of the patients. On CT two

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Table 1 Dementia and cerebral atrophy on CT scan in patients with primary degenerative dementia and patients with normal pressure hydrocephalus

	Dementia		Cortical atrophy			Ventricular enlargement		
	Moderate	Severe	None	Moderate	Severe	None	Moderate	Severe
Primary degenerative dementia (N = 16)	10	6	5	5	6	13	1	2
Normal pressure hydrocephalus (N = 18)	6	12	6	8	4	0	1	17

patients showed focal atrophy suggestive of a small cortical infarct, but they had no history of cerebrovascular disease and no symptoms of multi-infarct dementia. None of the patients had previous clinically recognised endocrine disorders. All medication was discontinued at least 3 days before examination. Lumbar puncture was performed between 9 and 11 am with the patients in the lateral recumbent position. The CSF pressure (11 ± 1 mm Hg (SEM)) was measured before removal of CSF samples of 5 ml. Blood samples for hormone and osmolality measurements were taken just before the lumbar puncture, after the patients had been recumbent for at least 30 minutes.

The group of 18 patients with normal pressure hydrocephalus comprised 11 men and 7 women aged 40 to 69 years, median age 59 years, with ventricular enlargement (hydrocephalus) in CT. All had clinical symptoms of dementia, gait disturbances and/or urinary incontinence (table 1). The cause of the normal pressure hydrocephalus was unknown in 10 patients, while four developed it following head trauma, three after subarachnoid haemorrhage and one after meningitis. None of the patients had clinical signs of endocrine diseases. In all patients a cannula was introduced into a lateral ventricle and the intraventricular pressure was continuously recorded via a catheter by a Statham 23 PM transducer during a 24 h period. At the end of this period a lumbo-ventricular perfusion study was performed.¹⁰ The intracranial pressure was normal (< 12 mm Hg) and the conductance to CSF outflow was decreased in all the patients (median 0.04 ml/min $\times$ mm Hg, range 0.01 – 0.09 ; normal value > 0.12 ml/min $\times$ mm Hg¹⁰). CSF samples were taken by lumbar puncture before the perfusion study, and blood samples just before the lumbar puncture.

The control group comprised 28 patients (15 men and 13 women, ages 20–66 years, median age 49 years) with symptoms of a cervical or lumbar disc syndrome, who were admitted for diagnostic myelography. Blood and CSF for analysis were taken in connection with the myelography performed between 9 and 11 am. None of the control patients had signs of cerebral or spinal cord diseases or

endocrine disorders, and they all had normal lumbar CSF pressure and normal CSF composition.

All patients were studied after informed consent had been obtained.

CSF and blood for hormone analysis 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. Plasma and CSF were stored at -20°C until AVP analysis was performed. Blood for osmolality measurement was taken in heparinised tubes. AVP in plasma and CSF was measured by radioimmunoassay after extraction with acetone and petroleum ether as previously described.¹¹ Detection limit of the analysis was 0.5 pg/ml, and the intra- and interassay coefficients of variation were 5–10% and 15%, respectively. 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 the Student's *t* test for unpaired data, analysis of variance, and the Mann-Whitney test.

Results

Mean AVP concentrations and osmolality in CSF and plasma are shown in table 2.

PATIENTS WITH PRIMARY DEGENERATIVE DEMENTIA

Mean CSF AVP concentration was lower in these patients: 0.9 ± 0.1 pg/ml (SEM), than in control patients ($p < 0.01$), (table 2 and fig 1). The CSF AVP concentration did not correlate with the severity of intellectual impairment or the degree of cortical or central atrophy on CT scan. Neither could the CSF AVP concentration be correlated with the age of the patient. Mean plasma AVP concentration was lower in the dementia group than in the normal-pressure hydrocephalus patients and controls ($p < 0.01$). As

Table 2 Vasopressin concentration and osmolality in CSF and plasma in patients with primary degenerative dementia, patients with normal pressure hydrocephalus and controls (Means $\pm$ SEM)

		Vasopressin conc (pg/ml)		Osmolality (m osm/kg H ₂ O)	
		CSF	Plasma	CSF	Plasma
Primary degenerative dementia	N = 16	$0.9 \pm 0.1^*$	$1.6 \pm 0.3^\dagger$	281 ± 2	285 ± 2
Normal pressure hydrocephalus	N = 18	1.2 ± 0.1	3.7 ± 0.6	281 ± 2	283 ± 2
Controls	N = 28	1.3 ± 0.1	3.6 ± 0.2	283 ± 1	287 ± 1

* $p < 0.01$ compared with CSF values in controls.

† $p < 0.001$ compared with plasma values in controls.

Fig 1 Cerebrospinal fluid vasopressin in 16 patients with primary degenerative dementia (PDD), 18 patients with normal pressure hydrocephalus (NPH), and 28 control patients (patients with cervical or lumbar pain syndromes).

Fig 3 Relationship between plasma osmolality and plasma vasopressin in 16 patients with primary degenerative dementia (PDD) (encircled dots indicate patients with marked cerebral atrophy) (a), 18 patients with normal pressure hydrocephalus (NPH) (b), and 28 control patients (c). The total range in normal subjects is indicated by the area between solid lines (ref 12).

no difference was found in plasma osmolality this could not explain the disparity in plasma AVP between the groups (table 2). The relationship between plasma osmolality and plasma AVP is shown in fig 3. Besides being lower, plasma AVP showed a poor correlation with plasma osmolality in the patients with dementia. Five out of the six dementia patients, who had marked cortical atrophy on CT scan, had plasma AVP concentrations outside the range found in normal subjects.¹²

PATIENTS WITH NORMAL PRESSURE HYDROCEPHALUS

Mean CSF A:VP concentration was 1.2 ± 0.1 (SEM) pg/ml which was not different from the value found in the control patients (table 2 and fig 1). Mean plasma

Fig 2 Relationship between plasma and cerebrospinal fluid vasopressin concentration in patients with primary degenerative dementia (a), normal pressure hydrocephalus (b), and controls (c).

AVP concentration was not different from that found in the control patients. In normal pressure hydrocephalus patients the normal correlation between plasma osmolality and plasma AVP was maintained, although five patients showed inappropriate high plasma AVP concentrations (fig 3).

CONTROL PATIENTS

Mean CSF AVP concentration was 1.3 ± 0.1 (SEM) pg/ml. In the control patients CSF AVP and plasma AVP were correlated, whereas no correlation was found between the two variables in patients with primary degenerative dementia or normal pressure hydrocephalus (fig 2). All control patients had plasma AVP concentration within the range found in normal subjects except for two, who had slightly elevated AVP levels (fig 3).

Discussion

Mean CSF AVP and plasma AVP concentration was lower in patients with primary degenerative dementia than the values found in controls and in patients with dementia associated with normal pressure hydrocephalus. The difference in CSF AVP between patients with primary degenerative dementia and normal pressure hydrocephalus could be explained by different pathophysiology of the dementia in the two disorders. Although the diagnosis of primary degenerative dementia in the present study was based on clinical signs only, no other causes of dementia were found in this group, and therefore the cognitive dysfunction was believed to originate from loss of neurons. In normal pressure hydrocephalus the dementia is probably caused by neuronal dysfunction rather than by neuronal loss, since the intellectual impairment can be improved by shunting procedures.¹³ The increase in CSF volume caused by hydrocephalus and/or cortical atrophy was judged from CT to be of comparable dimensions in primary degenerative dementia and normal pressure hydrocephalus patients, indicating that the low CSF AVP levels in primary degenerative dementia patients cannot be explained by a simple dilutional effect.

The subnormal CSF AVP in primary degenerative dementia could reflect a specific loss of neurons in an extrahypothalamic vasopressinergic system or be an insignificant phenomenon accompanying the widespread cerebral degeneration. Necropsy studies of brains from patients dying with a diagnosis of Alzheimer disease showed only little or no difference in AVP content in different locations of the brain.¹⁴ However, nuclear and nucleolar volume and cytoplasmic RNA in cells of the supraoptic and paraventricular nuclei were found to be reduced in patients with Alzheimer dementia, indicating a

reduction in protein synthetic capacity.¹⁵ This might be a contributory cause of the reduced CSF AVP in these patients, as vasopressinergic pathways from these regions can be traced to different parts of the central nervous system³ including the choroid plexus.²

Reduced CSF concentration of other neuropeptides (thyrotrophin-releasing hormone and gonadotrophin-releasing hormone) has been measured in patients with Alzheimer disease.¹⁶ Those findings together with the results of the present study give support to the view that the decrease in CSF concentration of different neuropeptides is a non-specific, coincidental phenomenon to the degenerative cerebral disease.

Using a radioimmunoassay for AVP measurements Tsuji *et al*¹⁷ suggested that CSF AVP concentrations were increased in patients with presenile and senile dementia (< 1.25 – 3.5 pg/ml, mean 1.8 pg/ml). This statement was based on a comparison with CSF AVP measurements in eight patients without dementia in whom CSF AVP was below detection limit of the assay (< 0.5 μ U/ml = < 1.25 pg/ml). Besides using an assay with a rather low sensitivity, this study differs from others in finding undetectable concentrations of AVP in CSF of control patients. Luerssen and Robertson¹ reported CSF AVP concentrations in normal subjects from 0.5 to 1.8 pg/ml, which is in accordance with our findings.

The results of therapeutic trials using AVP or synthetic analogs in the treatment of patients with memory disturbances and normal subjects have been conflicting. Some investigators reported improved memory function from vasopressin or synthetic analogs administered intranasally to patients with as well as without cognitive impairment.^{7,9} Others found no improvement of memory from vasopressin in Alzheimer patients¹⁸ or in patients with post-traumatic amnesia.¹⁹ However, the impermeability of the blood-CSF barrier to AVP makes it difficult to draw conclusions about the influence of CSF AVP on memory function from studies of intranasally administered AVP.

The results of plasma AVP measurements in the groups of demented patients suggest the presence of a defect in the osmoregulatory system and AVP secretion in some of these patients. In normal subjects the threshold for a rise in AVP secretion is a plasma osmolality about 280 mosm/kg, and above this threshold there is a linear relationship between plasma osmolality and AVP (fig 3).¹² Inappropriate concentrations of AVP in plasma^{20,21} and defects in osmoregulation of vasopressin secretion^{22,23} have been reported previously in patients with different cerebral lesions. Hyponatraemia caused by a lowered threshold of AVP release to increasing plasma

osmolality was described in patients with polyneuritis, possibly owing to disturbances of the peripheral volume receptors.^{24,25} A lowered threshold as well as increased sensitivity to changes in plasma osmolality was reported in a 41-year-old patient with severe dementia and marked cerebral atrophy.²³ Chronic hypernatraemia following cranial trauma²⁶ or encephalitis²³ was characterised by insensitivity of AVP release to increased plasma osmolality, but with a normal rise in plasma AVP after stimulation of the peripheral volume receptors.²⁶ This indicates an impairment of the afferent input of the osmoreceptors. Some of our patients with dementia had plasma AVP concentrations inappropriately high or low according to the corresponding plasma osmolality. It is, however, not possible from isolated measurements of plasma AVP and osmolality in the single patient to evaluate the nature of a possible defect in the osmoreceptor system. The central regulation of the osmoreceptors seems to be a rather complex system, probably under the influence of several parts of the central nervous system, and further studies are required to elucidate the exact nature of disordered osmotic regulation and AVP secretion in patients with diffuse cerebral lesions.

In conclusion we found plasma and CSF AVP concentrations lower in patients with primary degenerative dementia than in controls. Though these findings might encourage further clinical trials of AVP in patients with primary degenerative dementia, it must be emphasised that the low CSF AVP in these patients might be only a non-specific phenomenon accompanying the diffuse loss of cells in the central nervous system.

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