

Shunt related changes in somatostatin, neuropeptide Y, and corticotropin releasing factor concentrations in patients with normal pressure hydrocephalus

M A Poca, M Mataró, J Sahuquillo, R Catalán, J Ibañez, R Galard

Abstract

Objectives—Recent data indicate that alterations in brain neuropeptides may play a pathogenic role in dementia. Neuropeptide Y (NPY), somatostatin (SOM), and corticotropin releasing factor (CRF) are neuropeptides involved in cognitive performance. Decreased SOM and NPY concentrations have been found in patients with normal pressure hydrocephalus and are probably the result of neuronal dysfunction, which could potentially be restored by shunting. The effects of shunt surgery on preoperative SOM, NPY, and CRF concentrations were studied. Any improvements in neuropeptide concentrations that could lead to clinically significant neuropsychological and functional changes were also investigated.

Methods—A prospective study was performed in 14 patients with normal pressure hydrocephalus syndrome with a duration of symptoms between 3 months and 12 years. Diagnosis was based on intracranial pressure (ICP) monitoring and CSF dynamics. Concentrations of SOM, NPY, and CRF in lumbar CSF were determined before shunting and again 6–9 months after surgery. A battery of neuropsychological tests and several rating functional scales were also given to patients before and after shunting.

Results—After shunting, SOM and CRF concentrations were significantly increased in all patients. Concentrations of NPY were increased in 12 of the 14 patients studied. The clinical condition of 13 of the 14 patients was significantly improved 6 months after surgery. This improvement was more pronounced in gait disturbances and sphincter dysfunction than in cognitive impairment. No significant differences in any of the neuropsychological tests were seen for the group of patients as a whole despite the increased neuropeptide concentrations.

Conclusions—Shunting can restore SOM, NPY, and CRF concentrations even in patients with longstanding normal pressure hydrocephalus. However, despite the biochemical and clinical improvement in some areas such as ambulation and daily life activities, cognitive performance did not significantly improve. The role of

neuropeptides in the diagnosis and treatment of patients with normal pressure hydrocephalus syndrome is discussed.

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Keywords: normal pressure hydrocephalus; dementia; neuropeptides

Normal pressure hydrocephalus is a potentially treatable form of dementia. Several studies have indicated that intellectual impairment in patients with hydrocephalus may be mediated in part by a reduction in brain cholinergic function and by alterations in the noradrenergic and dopaminergic systems.^{1,2} In addition, various neuropeptides may also be involved in the modulation of cognitive processes.³⁻⁵

Neuropeptide Y (NPY), corticotropin releasing factor (CRF), and somatostatin (SOM) are neuropeptides that seem to produce or enhance cognitive performance, whereas galanin has been reported to inhibit cognitive processes.⁵ Patients with normal pressure hydrocephalus have significantly lower concentrations of SOM, NPY, and cholecystokinin in the CSF than control groups.⁶⁻⁸ Wikkelso *et al* also found that the concentrations of δ -sleep inducing peptide, vasoactive intestinal peptide, peptide YY, and SOM in 10 patients with normal pressure hydrocephalus were lower than those in controls and that the concentrations of some of these neuropeptides increased significantly after shunting.⁹ Recent research has also shown that shunting is able to reverse functionally injured neurotransmitter systems in hydrocephalic rats.² Because decreased concentrations of several neurotransmitters and neuropeptides in patients with normal pressure hydrocephalus are probably the result of neuronal dysfunction that can be restored by shunting, the aim of the present work was to study the effects of shunt surgery on SOM, NPY, and CRF concentrations. A further aim was to see whether any increases in neuropeptide concentrations would lead to neuropsychological and functional improvements.

Patients and methods

This study was approved by the institutional ethics committee on human research of Vall d'Hebron University Hospitals (Protocol number PR(HG) 114/97). Informed consent was obtained from the next of kin of patients included in the study.

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Table 1 Normal pressure hydrocephalus score¹⁰

	Score
Gait evaluation (GE):	
Patient is bedridden or not able to ambulate	1
Ambulation is possible with help	2
Independent walking is possible but unstable or the patient falls	3
Abnormal but stable gait	4
Normal gait	5
Cognitive functions (CF):	
Patient is vegetative	1
Severe dementia	2
Important memory problems with more or less severe behaviour disturbances	3
Memory problems reported by patient or family	4
Cognitive disturbances are only found by specific tests	5
Sphincter disturbances (SD):	
Urinary and faecal incontinence	1
Continuous urinary incontinence	2
Sporadic urinary incontinence	3
Urinary urgency	4
No objective or subjective sphincter dysfunction	5

NPH Score=GE+CF+SD. The minimum possible score is 3 points, and it indicates a patient that is bedridden or not able to ambulate, has a severe dementia (vegetative), and urinary and faecal incontinence. The maximum score of 15 points indicates a patient who has normal gait, cognitive disturbances only found by specific tests, and no objective or subjective sphincter dysfunction.

PATIENTS AND PROTOCOL OF STUDY AND SURGICAL MANAGEMENT

Of 25 consecutive patients with suspected normal pressure hydrocephalus evaluated in our department between June 1995 and September 1997, 14 were included in the study. Exclusion criteria were: (1) non-communication between the craniospinal compartments, (2) CSF samples contaminated by blood before and after shunting, (3) contraindications against lumbar puncture after shunting, and (4) patients' unwillingness to undergo repeat lumbar puncture.

Our protocol for the study and management of patients with suspected normal pressure hydrocephalus syndrome has previously been described in detail.¹⁰⁻¹¹ Briefly, patients were clinically graded according to the normal pressure hydrocephalus scale,¹¹ which evaluates the three main parts of the syndrome (table 1). Radiological assessment included several linear measurements of the ventricular system, such as the Evans ratio and the ventricular score (fig

1) obtained from CT or from MRI. All patients underwent continuous intracranial pressure (ICP) monitoring and studies of CSF dynamics. Monitoring of ICP was performed for at least 24 hours, including overnight recording, using a fiberoptic extradural device (LADD Research Industries Inc, Burlington, VT, USA). The CSF dynamics (resistance and conductance to outflow, pressure volume index, and compliance) were determined by Marmarou's bolus injection technique¹²⁻¹³ and the constant rate infusion test of Katzman and Hussey.¹⁴ All the patients had abnormal CSF dynamics and abnormal ICP waves (low and high amplitude B waves). A Delta valve with an incorporated antisiphon device (performance level of 0.5) was implanted in eight patients (Medtronic PS Medical, Goleta, CA, USA). A Hakim Medos valve system (closing pressure range 40 ± 10 mm H₂O; Medos SA, Switzerland), with an in line infraclavicular gravity compensating accessory (NMT Neurosciences Implants SA, USA) was implanted in the remaining six patients.

NEUROPSYCHOLOGICAL ASSESSMENT

Patients were given a neurological examination, a battery of neuropsychological tests to measure several aspects of verbal and visual memory, speed of mental processing, and frontal lobe functioning, as well as a brief screening battery for dementia. Each patient and a close relative were also given several rating scales to register the patient's functional behaviour and to assess changes in everyday activities (table 2). All these tests and behavioural scales were given by a research neuropsychologist to the patients while in hospital for presurgical investigation, and again 6 months later while attending hospital as outpatients.

CSF SAMPLES

A lumbar CSF sample (10 ml) was taken for biochemical study and analysis of neuropeptide concentrations before shunting and 6 months

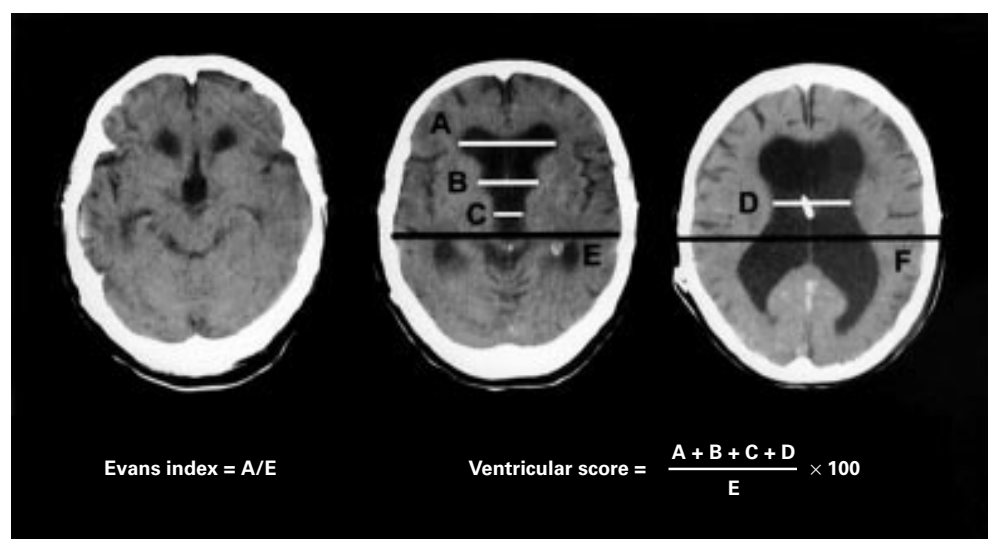


Figure 1 Measures of ventricular size on CT. (A) Maximum bifrontal distance. (B) Distance between the caudate nuclei at the level of the foramen of Monro. (C) Maximum width of the third ventricle. (D) Minimum width of both cella media. (E) Maximum inner diameter of the skull at the level of the measurement of the maximum bifrontal distance. (F) Maximum outer diameter of the skull at the level of the cella media.

Table 2 Neuropsychological tests and rating scales and questionnaires administered

Neuropsychological tests:
Wechsler memory scale
Trail making test A
Trail making test B
Word fluency
Mini mental state examination
Behavioural rating scales:
Informant's test
Normal pressure hydrocephalus score (NPH)
RDRS-2
Stein and Langfit
Everyday activities
DSMIII-R criteria of intensity of dementia
Clinical dementia rating

afterwards. The CSF was withdrawn from each patient between 8 00 and 10 00 am, after at least 8 hours of fasting and bed rest. To restore the basal CSF pressure, saline (10 ml) was injected immediately after withdrawing the CSF and before starting the study of CSF dynamics. The CSF was collected in plastic tubes containing Trasylol (1000 kIU/ml) to prevent proteolysis. Samples were immediately frozen at -20°C , and preserved at -80° , until assayed for SOM, NPY, and CRF immunoreactivity.

NEUROPEPTIDE ASSAYS

Immunoreactive CRF was measured by a competitive radioimmunoassay (Nichols Institute, CA, USA) after an extraction/concentration procedure with octadecasilyl silica columns (C_{18} Sep-Pak Waters, Milford, USA) in which 60% acetonitrile in 0.1% trifluoroacetic acid (Sigma Chemicals, CO, USA) for the peptide elution was used.¹⁵ The CRF antiserum showed 100% cross reaction with CRF (1–41) but no cross reaction with pre-pro CRF (125–151), adenocorticotrophic hormone (ACTH), luteinising hormone releasing hormone (LH-RH), or vasopressin. The detection limit of the assay was 2 pg/tube and the 50 binding intercept was 30 pg/tube. The extraction rate for plasma CRF was 62%.

To determine SOM and NPY concentrations, competitive radioimmunoassays (Incstar Corp, Stillwater, MI and Nichols Institute, CA, USA respectively) with an extraction/concentration method were used, as previously described in detail.^{7,8}

To avoid interassay variations, samples obtained both before shunting and between 6 and 9 months after the operation were determined

in the same run. The intra-assay coefficients of variation for CRF, NPY, and SOM assays were all less than 10%. Percentage change in neuropeptides equal to or less than 10% after shunting were not considered real changes.

STATISTICAL ANALYSIS

Statistical analysis was performed by non-parametric analysis. Preoperative and postoperative differences were analysed by the Wilcoxon matched pairs signed ranks test. Spearman's rank correlation test was performed to study the relation between neuropeptide concentrations and neuropsychological and behavioural functioning. The percentage change between basal and postoperative conditions was also determined: $((\text{postoperative} - \text{preoperative}) / \text{preoperative}) \times 100$. Differences were considered statistically significant at $p < 0.05$.

Results

DEMOGRAPHIC DATA

Fourteen patients (three women and 11 men) took part in our study. Their mean age was 66.4 years, range 55 to 79 years. Hydrocephalus was idiopathic in 13 patients and postmeningitic in the other. Patients dated the onset of their symptoms from 3 months to 12 years before admission. In all patients Hachinski's ischaemic score was below 4. Table 3 shows the most relevant preoperative and postoperative clinical and radiological information for each patient.

PREOPERATIVE FUNCTIONAL AND NEUROPSYCHOLOGICAL STATUS

Before treatment, only two patients were able to carry out daily life activities independently, eight patients required some supervision or help, and four were totally dependent or bedridden. Eight of the patients were mentally impaired with a mini mental state examination (MMSE) score of less than 25. In the Wechsler memory scale, six patients obtained normal memory scores (>85), four were mildly impaired (70–85), and four had severe memory deficits. The six patients with no or with only subtle memory disturbances had impaired psychomotor speed (trail making test A), attention, and mental flexibility (trail making test B). In two of these patients verbal fluency was also abnormal.

Table 3 Clinical, radiological, and biochemical information of each patient

Patient	Age/sex	Evolution (months)	NPH Scale Pre/post	EI Pre/post	VS Pre/post	SOM Pre/post % Change	NPY Pre/post % Change	CRF Pre/post % Change
1	79/F	12	10/15	0.40/0.41	97.8/102.9	29.7	25	144.19
2	55/F	60	9/12	0.43/0.37	115.5/91.9	1238.5	164.1	106.15
3	67/M	144	4/15	0.48/0.45	129.6/119.0	65.5	62.6	27.96
4	64/M	6	8/9	0.34/0.32	92.7/84.7	31.7	48.9	451.35
5	64/M	5	10/15	0.34/0.22	92.0/37.6	219.7	270.6	1037.5
6	62/M	5	14/15	0.40/0.19	114.3/37.7	120.9	20.3	45.27
7	60/M	3	7/11	0.40/0.34	111.1/89.4	120.4	42.9	—
8	70/F	60	8/14	0.37/0.38	101.3/97.0	55.5	48.6	60.84
9	60/M	13	13/13	0.36/0.36	91.5/87.3	30.4	-55.1	93.64
10	77/M	48	9/14	0.41/0.40	110.3/98.5	15.0	21.8	63.81
11	67/M	8	11/14	0.38/0.37	96.4/90.2	38.4	148.1	95.83
12	73/M	60	10/14	0.43/0.41	114.9/103.2	50.2	266.9	59.26
13	66/M	36	12/14	0.31/0.32	83.5/82.7	97.4	0	747.37
14	65/M	12	9/14	0.43/0.33	109.3/76.4	124.2	116.9	130

NPH=Normal pressure hydrocephalus; EI=Evans index; VS=ventricular score; SOM=somatostatin; NPY=neuropeptide Y; CRF=corticotropin releasing factor.

Table 4 Preoperative and postoperative values of variables in the battery of neuropsychological tests and in the behavioural scales

	Preoperative		Postoperative		p Value	% Change
	Median (IQR)	n	Median (IQR)	n		
<i>Neuropsychological tests</i>						
Memory quotient	88.50 (20.00)	12	84.50 (26.50)	12	NS	-4
Personal and current information	5.50 (2.25)	14	6.00 (1.25)	14	NS	0
Orientation	5.00 (2.25)	14	4.00 (1.25)	14	NS	0
Mental control	3.50 (3.25)	14	4.00 (3.75)	14	NS	0
Logical memory	6.25 (3.88)	14	5.00 (5.00)	14	NS	-21.24
Digit span forward	5.00 (2.00)	14	6.00 (2.00)	14	NS	0
Digit span backward	3.00 (4.00)	14	3.00 (4.00)	14	NS	0
Visual reproduction	4.00 (5.00)	14	3.50 (6.00)	14	NS	0
Associate learning	7.00 (5.50)	13	7.50 (2.13)	14	NS	0
Trail making test A	100.00 (112.00)	13	110.50 (97.75)	12	NS	8.33
Trail making test B	217.50 (68.50)	6	200.00 (82.50)	5	NS	16.21
Word fluency	12.00 (6.00)	13	10.50 (6.25)	14	NS	-17.65
Mini mental state examination	23.50 (7.75)	14	25.50 (8.25)	14	NS	2.78
<i>Behavioural scales</i>						
NPH Score	9.50 (3.25)	14	14.00 (2.25)	14	<0.01	45
NPH Gait evaluation	3.00 (1.00)	14	5.00 (0.00)	14	<0.01	76.67
NPH Cognitive functions	3.00 (1.00)	14	4.00 (1.00)	14	<0.01	33.33
NPH Sphincter disturbances	3.00 (1.50)	14	5.00 (0.50)	14	<0.01	66.67
RDRS-2	29.00 (8.75)	14	25.50 (7.25)	14	<0.05	16.41
Stein and Langfit	3.00 (2.00)	14	1.00 (1.00)	14	<0.01	150
Daily life activities scale	5.50 (4.50)	14	8.50 (3.00)	14	<0.05	25
Intensity of dementia (DSMIII-R)	1.00 (1.00)	14	1.00 (1.00)	14	NS	0
Clinical dementia rating	4.00 (4.38)	14	3.00 (2.63)	14	NS	12.50
Informant's test	65.00 (13.50)	13	51.00 (18.00)	13	<0.01	43.03

IQR=Interquartile range (the difference between the 25th and 75th percentile points); NPH=normal pressure hydrocephalus.

POSTOPERATIVE FUNCTIONAL AND NEUROPSYCHOLOGICAL CHANGES

Six months after shunting, most of the scales of daily life activities and the normal pressure hydrocephalus scale showed significant improvements (table 4). Twelve of the patients were able to cope with the tasks of daily life activities and the remaining two were only partially dependent. According to the normal pressure hydrocephalus score, 13 of the 14 patients improved after shunting (table 4). This improvement was more relevant in gait and sphincter functioning than in cognition (fig 2).

In the MMSE test, three patients presented an improvement equal or superior to four points and eight patients did not present any clinically significant change. After shunting, only six patients had an MMSE of less than 25. Although the shunt was working correctly, three patients presented a decrease of four or more points in this test and another patient performed worse than before on the Wechsler memory scale. However, when the patients were considered as a group, statistical analysis showed no significant change in any of the neuropsychological measures at 6 month follow up (table 4).

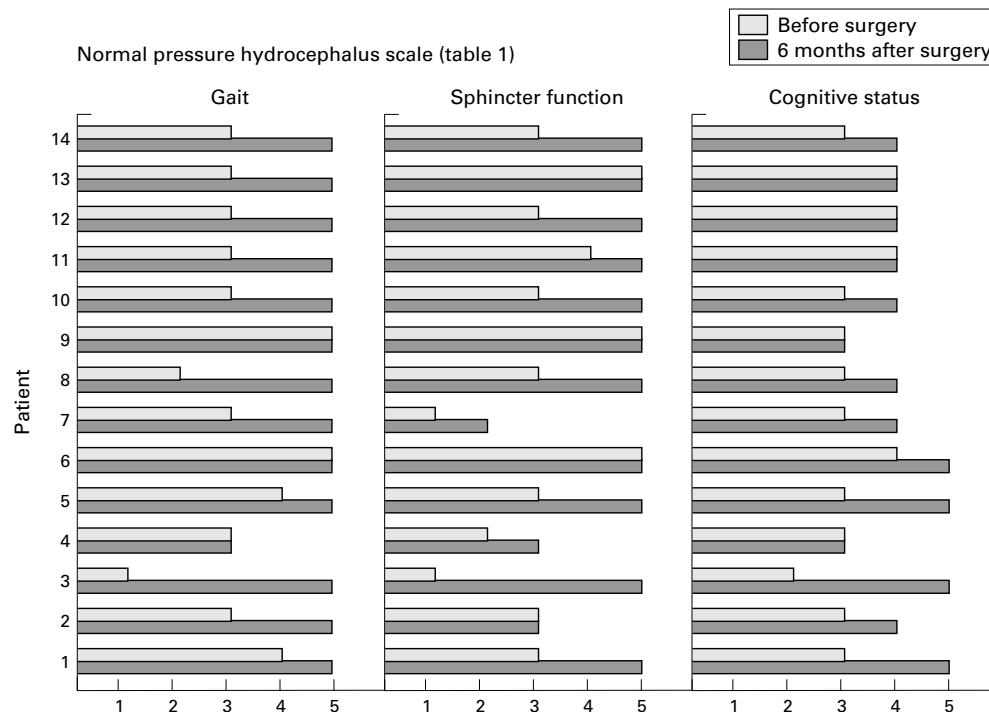


Figure 2 Basal condition and clinical condition after shunting of the patients, according to the normal pressure hydrocephalus scale. All patients improved after shunting. However, this improvement was more significant in gait disturbances and sphincter dysfunction than in mental impairment.

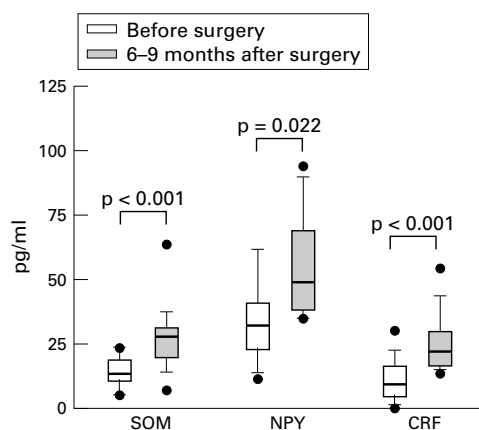


Figure 3 Box and whisker plot of neuropeptide concentrations before and 6 to 9 months after surgery. SOM=somatostatin; NPY=neuropeptide Y; CRF=corticotropin releasing factor.

NEUROPEPTIDE FINDINGS

The biochemical study and cell content of CSF, both before and after shunting, were within normal limits in all patients. After shunting, SOM concentration in the CSF of all patients significantly increased (28.09 (SD 12.9) pg/ml) above basal values (14.28 (SD 5.9) pg/ml). In one patient NPY concentrations were unchanged after shunting. In the remaining 13 patients NPY significantly increased from 30.5 (SD 10.7) pg/ml before shunting to 55.6 (SD 19.4) pg/ml after shunting. Basal and postoperative CRF concentrations were tested in 13 patients; shunting significantly increased CRF concentration from 12.13 (SD 8.1) pg/ml before shunting to 26.3 (SD 11.7) pg/ml after shunting (fig 3). Table 3 shows the percentage change in the three different neuropeptides for individual patients.

Basal values of SOM correlated positively and significantly with visual memory performance ($r=0.57$; $p=0.032$) and speed of mental processing as tested by the trail making test A ($r=-0.55$; $p=0.050$). Percentage change in SOM concentrations correlated significantly with percentage change in the rapid disability rating scale-2 (RDRS-2) test, which measures certain daily life activities ($r=0.66$; $p=0.010$). Percentage change in NPY concentrations correlated with percentage change in the RDRS-2 test ($r=0.62$; $p=0.018$). Percentage change in CRF concentrations correlated negatively with percentage change in postoperative verbal fluency ($r=-0.57$; $p=0.053$) and with percentage change in the trail making test B ($r=-1$; $p=0.000$). However, only three patients were able to complete the trail making test B.

No significant relation was found between the percentage reduction of the ventricular indexes after shunting and the percentage change of SOM, NPY, and CRF concentrations. Similarly, there was no significant correlation between the percentage change in protein content of CSF and the reduction in ventricular size, nor was there any relation between time of evolution and the percentage change in neuropeptide concentration.

Discussion

This study shows that SOM, NPY, and CRF concentrations in lumbar CSF increase in most patients with normal pressure hydrocephalus after shunting and that recovery of these neuropeptide concentrations is associated with clinical improvement in specific areas such as ambulation and tasks of daily life activities but not in cognitive performance.

NEUROCHEMICAL ABNORMALITIES IN THE CSF OF PATIENTS WITH HYDROCEPHALUS

Alterations in the neurochemical composition of CSF due to hydrocephalus have been widely documented and reviewed.¹⁶ Significantly lower concentrations of δ -sleep inducing peptide, peptide YY, cholecystokinin, SOM, and NPY have been reported in the lumbar CSF of patients with normal pressure hydrocephalus.⁶⁻⁹ However, in patients with altered CSF volume and dynamics, the relevance of these findings is still being debated.

One controversy concerns whether the low values of neuropeptides in the CSF of patients with hydrocephalus are artefacts. Wikkelsö *et al* have noted that in hydrocephalic patients, low neuropeptide values in the CSF can be caused not only by reduced release or increased degradation but also by an altered distribution volume of the CSF.⁹ In our study, CSF protein concentrations were evaluated before and after shunting in all patients. Unlike neuropeptide concentrations, CSF protein concentrations were within normal limits in all patients before surgery, despite increased ventricular volume. After surgery protein concentrations increased beyond the normal range in six patients. All of these six patients had marked ventricular dilation before shunting (Evans index 0.34–0.48). However, reduction in ventricular size varied among the patients: one patient showed no change, three patients showed a slight change, and two patients showed a large reduction. No significant correlation was detected between percentage change in protein concentrations and reduction in ventricular size. These results were similar to those of Wikkelsö *et al*.⁹ Equally, no significant correlation was detected when we analyzed percentage change in SOM, NPY, and CRF concentrations and percentage change in reduction of ventricular indexes. The initial normality in CSF protein concentrations as well as the lack of correlation between the percentage of changes in the various peptide and protein concentrations and the reduction in ventricular size argue against the validity of the dilution theory.

Another controversial aspect of studies on concentrations of neuropeptides measured at the lumbar level is the presence of gradients between ventricular and lumbar CSF in several neurotransmitters and neuropeptides.^{17,18} However, measurements of the lumbar CSF concentrations of different substances have been an important research tool for several years, and the accuracy of this approach has been repeatedly corroborated both in experimental and clinical studies by parallel determinations of brain tissue and CSF peptide concentrations.^{19,20} In the present study, CSF

was obtained before and after shunting at the same lumbar level and also at the same time of day to eliminate the effects of different locations and possible circadian rhythms on the neuropeptides studied.

FUNCTIONAL AND NEUROPSYCHOLOGICAL IMPROVEMENT AFTER SURGERY

Five of the 14 patients in our series had had symptoms for more than 12 months. Nevertheless, the clinical evaluation 6 months after shunting showed that 13 patients had improved in functional grade according to the normal pressure hydrocephalus score. This improvement was also significant in the daily life activities scale, which registers the magnitude of functional capacity of patients according to how much help they need to carry out different daily life activities (mobility, shopping, cooking, household tasks, and money management). These results confirm that shunting in patients with longstanding normal pressure hydrocephalus can help them to become more independent and can improve their quality of life. By contrast, no significant differences between preoperative and postoperative neuropsychological tests were seen in any test for the group of patients as a whole. However, as many patients had only mild cognitive impairment, the lack of a significant difference between preoperative and postoperative periods could also have been due to a ceiling effect.

In five of the 14 individual patients cognitive performance improved considerably. However, in four other patients, with a clear improvement in gait disturbance and in sphincter control, cognition was worse after surgery. There is a strong possibility that these patients had mixed dementia, as has been suggested in other studies.²¹ Excluding these patients from the analysis produced a significant improvement in a subtest of the Wechsler memory scale (personal and current information, $p=0.043$) and MMSE ($p=0.028$), and a marked improvement in logical memory ($p=0.059$). According to these data, if the sample had been larger, the results of all the evaluated tests could well have been positive.

SOMATOSTATIN CONCENTRATIONS IN THE CSF OF PATIENTS WITH NORMAL PRESSURE HYDROCEPHALUS

In a previous study,⁸ the mean SOM value found for normal subjects in our laboratory was 24.8 (SD 12) pg/ml. In the present study the mean SOM value in patients with normal pressure hydrocephalus after shunting (28.09 (SD 5.9) pg/ml) was similar to that of normal subjects, except in one patient in whom SOM values remained below normal. The basal (preshunt) SOM concentrations in four patients was very low, whereas in the remaining patients the degree of neuropeptide loss was less severe. This reduction of SOM concentrations in patients with normal pressure hydrocephalus has been confirmed by other authors.^{22,23} In hydrocephalus, the decrease in this neuropeptide could be attributed to the fact that SOM is highly concentrated in the cortical neurons and in the nerve terminals of the hypothalamus; these

structures are selectively impaired in experimental hydrocephalus.^{1,24} In a previous paper, we were unable to see a positive correlation between MMSE and SOM values in the CSF of five patients with normal pressure hydrocephalus. In the present series, we found that basal values of SOM correlated significantly with visual memory performance and visuomotor speed, suggesting that higher concentrations of SOM were associated with better visual memory and increased speed of mental processing. However, these associations did not persist after surgery. After shunting, percentage change in SOM concentrations correlated significantly with percentage improvement in the test of daily life activities (RDRS-2), as well as in the test of attention and mental flexibility (trail making test B). More studies are needed to elucidate the true role of SOM in cognition.

NEUROPEPTIDE Y CONCENTRATIONS IN THE CSF OF PATIENTS WITH NORMAL PRESSURE HYDROCEPHALUS

Normal or decreased concentrations of NPY have been found in the lumbar CSF of patients with Alzheimer's disease.²⁵⁻²⁷ However, none of the authors found any correlation between NPY values and the severity of dementia.²⁵⁻²⁷ In a previous paper, we showed that values of NPY in the CSF of patients with normal pressure hydrocephalus were significantly lower than in controls and that neither the MMSE nor the results of the Blessed dementia scale showed a significant correlation with NPY in these patients.⁷ In the present series of 14 patients with a confirmed diagnosis of normal pressure hydrocephalus, we again found that basal values of NPY did not correlate either with dementia or with any neuropsychological function tested. After shunting, NPY increased significantly in 12 of the 14 patients and the percentage change in NPY concentration correlated only with a functional/behavioural scale (RDRS-2). The postshunt concentrations of this peptide (mean 55.6 (SD 19.5) pg/ml) were clearly lower than the control values found in our laboratory (mean 117.3 (SD 33.4) pg/ml).⁷ This indicates that, after shunting, recovery of NPY concentrations in the affected brain regions is less marked than recovery of SOM. For individual concentrations, NPY concentrations in CSF persisted below control concentrations in 50% of patients. For basal values, we obtained NPY concentrations in CSF lower than those described for patients with normal pressure hydrocephalus in our laboratory (mean 64.5 (SD 25.1) pg/ml),⁷ which confirms the marked deterioration in the NPY dependent neuronal systems in these patients.

CORTICOTROPIN RELEASING FACTOR CONCENTRATIONS IN THE CSF OF PATIENTS WITH NORMAL PRESSURE HYDROCEPHALUS

To our knowledge, this is the first study to evaluate CRF concentrations in the CSF of patients with normal pressure hydrocephalus. In these patients, the significant increase in the concentration of CRF after shunting could be explained by an improvement in cerebral blood

flow and metabolism, especially in the frontal cortex. Despite this increase, however, CRF concentrations in the CSF remained below the normal reported range (from 40 to 65 pg/ml).²⁵⁻²⁸ The preshunt (mean 12.13 (SD 8.1) pg/ml) and postshunt (mean 26.3 (SD 11.7) pg/ml) values obtained in our patients suggest a considerable alteration of this neuropeptide in some areas of the CNS, even after shunting.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

These results and those of previous studies,^{6-7,9} suggest that patients with normal pressure hydrocephalus syndrome can present a non-specific decrease in brain neuropeptides as a result of global neuronal dysfunction. The decrease is probably greater in molecules which originate in the periventricular areas and in the brain cortex and is less marked in neuropeptides located mainly in the brain stem and the spinal cord.¹⁻⁹ However, given that patients with normal pressure hydrocephalus, as well as those with Alzheimer's disease or other neurodegenerative disorders, can present a similar pattern of neuropeptide abnormalities, caution should be used when considering a decrease in neuropeptides as a specific diagnostic criterion.

The most important finding of this study was that shunting patients with a long history of idiopathic normal pressure hydrocephalus can increase the concentration of several neuropeptides. These results lend additional support to the validity of treating patients with longstanding idiopathic normal pressure hydrocephalus. Nevertheless, the biochemical and clinical improvement seen in our study in specific areas, such as waking and sphincter dysfunction, contradict the results of some experimental studies, in which neurotransmitters were only restored in animals shunted before the 4th week of evolution.² In our patients, despite the significant biochemical changes and functional improvement, the cognitive performance of only a few patients improved. This discrepancy, which has been noted by other authors,²⁹ could be explained by an insufficient increase in neuropeptide concentrations to correct cognitive impairment, or because the dysfunction may be located in the receptors. Given the state of current knowledge, however, the most plausible explanation is an irreversible alteration in certain synapses, as has been shown to be the case in experimental studies.³⁰ Future studies should be undertaken to elucidate these possible physiopathological alternatives and to determine whether or not the decrease in neuropeptide concentrations is merely a biochemical epiphenomenon.

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