High resolution SPECT with [^{99m}Tc]-*d,l*-HMPAO in normal pressure hydrocephalus before and after shunt operation

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Abstract

Cranial CT and high resolution measurements of regional cerebral blood flow (rCBF) with brain dedicated single photon emission computer tomography (SPECT) and [^{99m}Tc]-*d,l*-hexamethyl-propyleneamine oxime ([^{99m}Tc]-*d,l*-HMPAO) were performed before and after shunt operation in 14 consecutive patients with dementia and normal pressure hydrocephalus (NPH). When compared with a control group of 14 age matched healthy volunteers, the group of NPH patients was characterised by an enlarged subcortical low-flow region, significantly reduced rCBF and enhanced side-to-side asymmetry of rCBF in the central white matter, and enhanced side-to-side asymmetry in the inferior and mid-temporal cortex. Global CBF was normal. Shunt operation reduced the mean area of the ventricles on CT and of the subcortical low-flow region on SPECT. Global CBF was unchanged. All 14 patients had an abnormal pre-shunt rCBF pattern with enlargement of the subcortical low flow region, focal cortical blood flow deficits, or both. Shunt operation improved the clinical status in 11 patients, and the area of the subcortical low flow region correctly classified 3/3 unimproved and 10/11 improved patients. Shunt operation normalised or reduced the area of the subcortical low flow region in nine of 10 patients. It is concluded that SPECT with [^{99m}Tc]-*d,l*-HMPAO is a useful supplement in the diagnosis of NPH versus normal ageing, and that SPECT may help to identify patients not likely to benefit clinically from surgery.

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Normal pressure hydrocephalus (NPH) is a rare, but potentially treatable cause of dementia. It was described in 1965 by Hakim and Adams[1] and Adams *et al*[2] as a syndrome involving: 1) progressive dementia characterised by memory impairment and psychomotor retardation; 2) disturbance of balance and gait with rigidity or spasticity of lower limbs, and 3) impaired control of sphincters, in patients with enlarged ventricles and normal CSF pressure. Permanent drainage of the CSF was proposed as a treatment.[1 2] Intensive research has aimed at improving the clinical, radiographic, and hydrodynamic criteria used as indications for shunt operation. On the assumption that the pathogenesis of NPH involves impaired absorption capacity of the CSF system and thus a reduced conductance to outflow of CSF (C_{out}), Børgesen *et al*[3] described a method for its determination. They concluded that only patients with $C_{out} < 0{\cdot}08$ ml·mm Hg^{-1}·min^{-1} (or resistance to outflow, $R_{out} > 12$ mm Hg·min·ml^{-1}) might benefit from shunt operation.[4]

As reviewed by Turner and McGeachie,[5] the percentage of selected patients who improved after CSF shunting has been reported to be in the range 25–80%. This response rate must be reviewed in the context of a 30–40% postoperative complication rate, including anaesthetic complications, infections, intracranial haematomas, and shunt malfunctions.[5] The clinical differentiation of mild NPH from normal ageing, benign senile forgetfulness, Alzheimer's disease, or other degenerative dementia disorders, which may be associated with enlarged ventricles and perhaps similar symptoms, is difficult. Better diagnostic studies might improve the predictive power of clinical improvement.

The aim of this study was to investigate the value of high resolution single photon emission computer tomography (SPECT) of regional cerebral blood flow (rCBF) using [^{99m}Tc]-*d,l*-hexamethyl-propyleneamine oxime ([^{99m}Tc]-*d,l*-HMPAO) in the diagnosis of NPH versus normal ageing and in the prediction of the clinical outcome after shunt operation in NPH. Furthermore, the effect of shunt operation on cortical and subcortical rCBF was analysed.

Patients and methods

Patients

Fourteen patients (four women, 10 men) with NPH were included in the study. Their median age was 64 years (range: 24–84). Their clinical and hydrodynamic data are presented in table 1. The patients were consecutively admitted to the Department of Neurosurgery and selected for shunt operation. In two patients the NPH condition had developed secondary to a subarachnoid haemorrhage (SAH), in two other patients possibly to a previous head trauma, and in one patient to an arterial aneurysm. In the remaining nine patients the aetiology was unknown. The median duration of symptoms was 18 months (range: 1–36). All patients

Table 1 Normal pressure hydrocephalus: Clinical, hydrodynamic, and CT data

Clinical data					*Hydrodynamic data*			*CT data*				
Case	*Age/sex*	*Aetiology*	*Duration*	*symptoms D G U*	*mICP*	*B-waves*	R_{out}	*Cortical atrophy*	*Ventricle size*	*Evans' ratio*	*PVL*	*Focal abnormalities*
1	63/F	unknown	18	+ + +	10	30	21·2	6	2/0	0·32/0·28	+	none
2	64/M	SAH[1]	18	+ + −	8	100	14·9	7	1/1	0·35/0·31	+	subcortical infarcts
3	24/M	unknown	12	+ − −	10	5	23·2	0	4/0	0·31/0·27	−	none
4	45/M	unknown	36	+ − −	9	30	20·8	2	4/4	0·32/0·29	−	none
5	63/F	unknown	24	+ + +	12	30	15·2	8	6/6	0·44/0·37	+	subcortical infarct
6	24/F	SAH[2]	1	+ + −	8	40	52·0	0	4/3	0·47/0·30	−	tissue loss, frontal
7	51/M	head trauma	24	+ + −	12	100	16·2	0	6/6	0·50/0·48	−	none
8	73/M	unknown	6	+ + +	8	100	23·3	4	4/0	0·42/0·28	+	1 small infarct[4]
9	71/M	unknown	36	+ + −	12	10	14·7	8	2/2	0·32/0·30	+	none
10	69/M	aneurysm[3]	2	+ + +	12	10	31·3	2	4/NA	0·33/NA	+	aneurysm[3]
11	72/F	unknown	9	+ + +	9	70	30·0	4	6/1	0·44/0·33	+	none
12	84/M	unknown	36	+ + +	11	60	21·2	10	4/5	0·48/0·42	+	none
13	51/M	unknown	24	+ + +	10	80	20·4	1	6/1	0·52/0·29	+	none
14	66/M	head trauma	6	+ + −	12	25	47·0	2	4/4	0·46/0·40	+	none

duration = duration of symptoms in months; symptoms: D = dementia; G = gait disturbance; U = urinary incontinence; mICP = resting mean intracranial pressure given in mm Hg; B-waves = duration of B-waves given in % of recording time (24 hrs); Rout = resistance to outflow for cerebrospinal fluid (mm Hg min ml^{-1}); cortical atrophy = rating of cortical atrophy, maximum = 30 (see text); ventricle size = rating of ventricle size before/after shunt, maximum = 6 (see text); Evans' ratio = ratio of the maximum width of the frontal horns of the lateral ventricles to the maximal internal diameter of the skull; PVL = periventricular leucoencephalopathy. 1) traumatic subarachnoidal haemorrhage; 2) subarachnoidal haemorrhage from aneurysm of anterior communicant artery; 3) aneurysm of vertebral and basilar artery; 4) right anterior watershed area; NA = not available (patient died)

presented with dementia, in most cases associated with gait disturbance or urinary incontinence.

A 24 hour monitoring of intracranial pressure was performed before surgery. The mean intracranial pressure (ICP), and the duration of B-waves were recorded. The resistance to outflow of CSF, R_{out}, was calculated from data obtained in a lumboventricular perfusion study.[3] The diagnosis of NPH was based on the history and clinical examination, enlarged ventricles on CT of the brain (Evans' ratio[6] > 0·30), and mean ICP < 15 mm Hg. The indication for ventriculo-peritoneal shunt operation was based on the finding of a R_{out} greater than 12 mm Hg·min·ml^{-1}.[4] A Hakim medium or an Orbis-Sigma shunt was used in all patients. The functional status of each patient was rated on a 5 grade scale, a modification of the Stein-Langfitt functional scale[4 7]: 0 = no neurological deficit, able to work; I = minimal deficit, able to function independently at home; II = some supervision required at home; III = custodial care required in spite of considerable independent function; IV = no practical capacity for independent function; V = vegetative, bedridden, no spontaneous activity, no verbal contact. The functional grading was performed by one of the authors (JFS) who was not acquainted with the SPECT results. SPECT and CT of the brain were repeated together with the functional grading 3–6 months after the shunt operation. All patients (or relatives) gave informed consent to the study which was approved by the local ethical committee.

Control subjects

The results of CT and SPECT were compared with those of 14 age- and sex-matched healthy and neurologically normal volunteers (four women and 10 men) from a normal group, described in detail elsewhere.[8] Their median age was 63 years (range: 22–83).

CT

CT of the brain was obtained in all patients with a Somatom DR2 scanner (Siemens, Germany) or an EMI 1000 scanner (Medical Hounslow, UK). Contiguous transverse CT slices 8 mm (Somatom DR) or 10 mm (EMI 1000) thick and parallel to the cantho-meatal (CM) plane were obtained. The pre- and postoperative CT scans from the patients were randomly mixed with CT scans from the control subjects and evaluated blindly by one of the authors who did not know the diagnosis and the age of the patient, or the results of the SPECT scan. All scans were carefully studied for any focal abnormalities. The ratio of the maximum width of the frontal horns of the lateral ventricles to the maximum internal diameter of the skull, the Evans' ratio,[6] was measured. The size of the ventricles was rated on a 0–3 point scale (0 = small or normal, 1 = mildly enlarged, 2 = moderately enlarged, 3 = severely enlarged).[9] On preoperative CT films, the degree of cortical atrophy was rated on a 0–3 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), relating to the size of the sulci in five cortical regions (frontal, temporal, parietal, insulae, occipital) in each hemisphere.[9] The scores were summed to calculate the total cortical atrophy score.

The area of the ventricles relative to the total intracranial area was measured parametrically on three midbrain slices (slices number 4, 5, and 6): the relevant CT film images were placed on a radiograph view box. The perimeter of the ventricles and the inner surface of the cranium were traced onto tracing paper, and a personal computer scanner was used to produce a digitised image on a computer screen.[8 10] The surface area of the ventricles relative to the total intracranial area (V/C%) was calculated by a computer program.

SPECT

Regional CBF was measured by two methods consecutively on the same day: by the low resolution ^{133}Xe-inhalation method and by high resolution static imaging of the distribution of an intravenous dose of [^{99m}Tc]-*d,l*-HMPAO. The activity in the brain was measured by the Tomomatic 64 (Medimatic, Hellerup, Denmark), a rapidly rotating and highly sensitive three slice instrument for brain SPECT, described in detail previ-

ously.[11] All scans were obtained in parallel to the CM plane, and the patients were studied in the supine position during rest with eyes closed and with ears unplugged in quiet surroundings.

The ^{133}Xe-inhalation study lasted 4·5 minutes and was performed to obtain quantitative rCBF data. With this technique the in-plane resolution is 17–20 mm (full width at half maximum, FWHM) and the slice thickness 20 mm. The calculation of CBF from a sequence of 4 time activity pictures was based on a combination of the isotope clearance principle and the bolus distribution principle.[12] At the end of the study the end-expiratory CO_2-fraction ($FECO_2$) was measured using a capnograph (CDA-1 CO_2-analyser, Novo Diagnostic Systems, DK). Two patients were unable to cooperate in the inhalation procedure.

Before the [^{99m}Tc]-*d,l*-HMPAO study, ^{99m}Tc pertechnetate was eluated from a Mo-Tc generator and mixed with *d,l*-HMPAO (Exametazime, Ceretec^R, Amersham, UK). A bolus containing 1·1 GBq [^{99m}Tc]-*d,l*-HMPAO was injected intravenously. The acquisition time was approximately 25 minutes yielding at least $3 \cdot 10^6$ counts per slice. In as many patients as possible, data acquisition was performed in three different positions to obtain nine contiguous image slices covering the whole brain. In three cases, however, it was not possible to obtain more than one data set with three slices due to poor patient cooperation. Following reconstruction, the data were normalised to the cerebellum and corrected to adjust for incomplete retention of the tracer by the algorithm suggested by Lassen *et al*[13] using a conversion/clearance ratio of 1·5. The cerebellar hemisphere with the highest countrate was used as the reference region, and its countrate was determined by a lower 60% fractile threshold.[8]

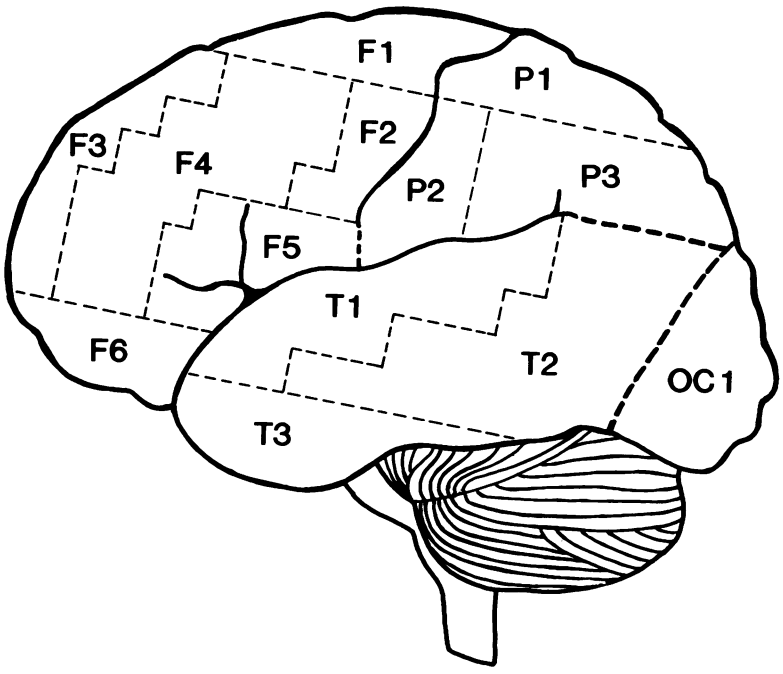

Figure 1 Schematic drawing of a lateral view of the left hemisphere with localisation of the cortical regions of interest. F = frontal cortex, F1 = upper frontal cortex; F2 = precentral gyrus; F3 = superior frontal gyrus and cingulate gyrus; F4 = middle frontal gyrus; F5 = inferior frontal gyrus; F6 = orbito-frontal gyrus; T = temporal cortex; T1 = superior temporal gyrus and insula cortex; T2 = inferior and middle temporal gyrus; T3 = temporal poles; P = parietal cortex; P1 = upper parietal cortex; P2 = postcentral gyrus; P3 = supramarginal and angular gyrus; OC = occipital cortex; TH = thalamus; LN = lenticular nucleus; CD = caudate nucleus; HC = hippocampus. Reproduced, with permission, from Waldemar et al. 1991.[8]

Both studies were repeated, if possible, after shunt operation. Of the 11 patients with a full 9-slice preoperative study, nine patients also had a full 9-slice postoperative study, one had died (case 10) and one was unable to cooperate to more than one 3-slice data acquisition (case 1).

Analysis of rCBF data

With the ^{133}Xe-inhalation method three slices were obtained. Mean cerebellar blood flow was calculated from the lowest slice, and mean blood flow in the cerebral hemispheres was calculated from the mid-brain slice as the mean of all brain pixels. Fixed templates were used to calculate rCBF in a few cortical regions of interest.

In patients with a full 9-slice SPECT study, the analysis of the rCBF data from the [^{99m}Tc]-*d,l*-HMPAO study was performed by assigning 1 of the 10 reference atlas[14] CM levels to each rCBF slice. Guided by the assigned anatomical slice and its preconstructed ROI template, ROIs were placed on each rCBF map after adjusting for size and shape of the brain slice.[8] The presentation of ROIs in relation to the lateral brain surface is shown in fig 1. The mean pixel value ($F_{i,s}$) and the area of each ROI (i) in the number of pixels were calculated.[8] For ROIs appearing in more than one slice in the same subject, a weighted mean flow value was calculated for the left ($F_{i(L)}$) and the right ($F_{i(R)}$) ROI. The side-to-side asymmetry index, SAI, was defined as:

$$SAI_i(\%) = 100 \times \frac{F_{i(R)} - F_{i(L)}}{F_{i(max)}}$$

where F_i(max) is the blood flow in the higher of the two ROIs. Anterior/posterior ratios were calculated as the ratio of the mean rCBF in the frontal cortex to the mean rCBF in the temporal cortex (F_F/F_T) or the parietal cortex (F_F/F_P).

In all subjects a subcortical low flow area[8] was defined as shown in fig 2 from the 3 mid-brain slices (slices 4, 5, and 6) as all intracerebral pixels with values lower than a preselected low flow threshold, τ, defined from the peak pixel value, F_{peak}, of the slice as

$$\tau = 50 + 0{\cdot}20 \times (F_{peak} - 50)$$

The relative area of the subcortical low flow region, and the mean rCBF in the surrounding high flow cortical rim, were calculated and compared with the parametric measurements on the corresponding CT slices.[8]

Statistical methods

Data from the NPH and control groups were compared using the Wilcoxon two sample test. Data from before and after shunt operation were compared using the Wilcoxon

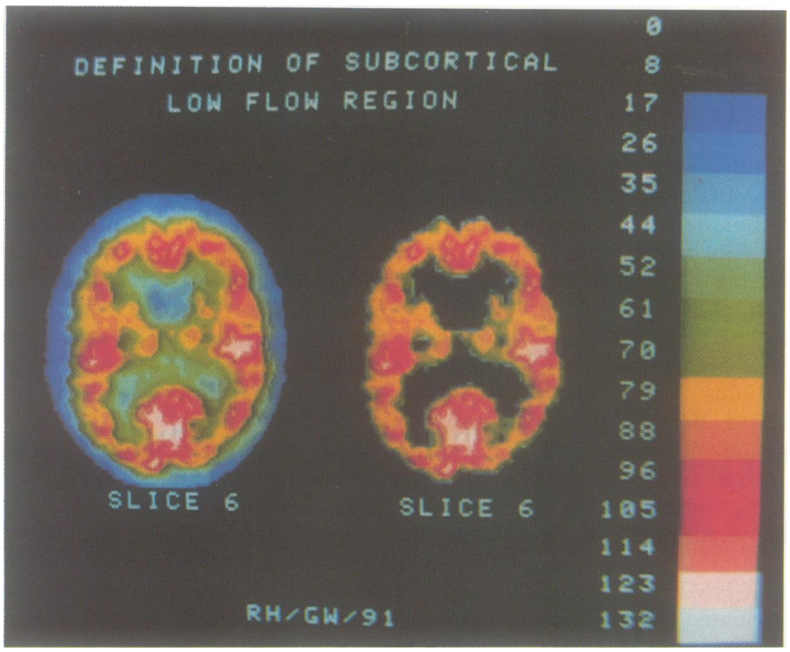

Figure 2 SPECT with [^{99m}Tc]-d,l-HMPAO (slice 6) in a 51 year old healthy male. The left hemisphere is shown to the left. The colour scale indicates relative regional cerebral blood flow (F(%)) values (from 0 to 140%) calculated from corrected relative countrates normalised to the cerebellum. The peak pixel value of this slice was 136% and the low flow threshold 67%. As shown to the right this threshold defined a subcortical low flow region (black), including the ventricles and periventricular tissue, and a surrounding cortical high flow region. The relative area and the mean rCBF of each region was calculated by the computer.

paired test. The level of statistical significance was set at $p = 0{\cdot}05$. To adjust for the effect of multiple comparisons, a Bonferroni correction was applied to the statistical p values for differences in rCBF and SAI (NPH versus control, and post-shunt versus pre-shunt) in the 17 cortical subregions shown in fig 1.

In the analysis of rCBF patterns in individual patients, CBF parameters (SAI values from large cortical ROIs (F, T, P, and OC), anterior-posterior ratios, and parameters from the subcortical low flow region) were characterised as significantly abnormal if they deviated by at least 2 SD from control mean. The diagnostic sensitivity and specificity of a given parameter in determining surgical outcome was defined as the predictive value of a normal and a significantly abnormal result (that is, deviation more than 2 SD from control mean), respectively.

Results

Clinical outcome

There were three patients with grade I, four with grade II, five with grade III, and two with a grade IV functional status (table 2). One patient (case 10) died before the postoperative study. Eleven of the remaining 13 patients improved (85%). Seven had a good clinical outcome (functional grade reduced to 0 or by at least two steps), and four patients had a moderate effect (functional grade reduced by one step) of the operation. Two patients had a poor clinical outcome (functional grade increased) after the operation, despite a well functioning shunt. The aetiology of NPH in these two patients was unknown. Two patients needed re-operation because of shunt malfunction (case 7) or infection (case 5). All seven patients with more than 30% B-waves improved after shunt operation.

Cranial CT

CT data for individual patients are shown in table 1. Ten of 14 patients had periventricular white matter abnormalities (lining, "halo" or irregular periventricular leuco-encephalopathy), in two it was associated with small subcortical infarcts.

As already determined in the selection of patients, the ventricles were significantly enlarged in the patients with NPH. The median rating score was 4 (range 1–6) as compared with 0 (range 0–4) in the control subjects ($p < 0{\cdot}01$). The Evans' ratio was also significantly ($p < 0{\cdot}01$) higher in the NPH group, median 0·43 (range 0·31–0·52), than in the control subjects, median 0·29 (range 0·24–0·33). When an Evans' ratio at or above control mean + 2 SD (= 0·35) was taken as abnormal, the diagnostic sensitivity and

Table 2 Clinical function and regional SPECT abnormalities[1] in patients with NPH before and after shunt operation

	Clinical function[2]			*Cortical rCBF deficits[3]*			*Subcortical low flow region on SPECT and ventricles on CT[6]*			
Case	*Before*	*After*	*Effect*	*A/P ratio[4] Before*	*abnormal SAI[5] Before*	*After*	*Before SC/C*	*V/C*	*After SC/C*	*V/C*
1	II	III	no	F/P ↓	frontal	(NA)	**+ 0·5**	+ 3·4	**−0·3**	+ 4·4
2	II	I	moderate	F/P ↓	frontal, parietal, and temporal	no change	**+ 1·6**	+ 2·9	**+ 1·3**	+ 2·5
3	I	0	good	(NA)	(NA)	(NA)	+ 2·3	+ 2·4	**+ 1·3**	**+ 0·9**
4	I	0	good	(NA)	(NA)	(NA)	+ 2·2	+ 4·4	+ 2·1	+ 3·1
5	III	II	moderate	F/P ↑	occipital	normal	+ 3·8	+ 12·5	+ 3·0	+ 9·4
6	IV	II	good	(NA)	(NA)	(NA)	+ 5·1	+ 3·8	**+ 0·1**	+ 3·8
7	I	0	good	normal	none	normal	+ 3·2	+ 10·2	+ 2·9	+ 9·4
8	III	II	moderate	F/P ↓	frontal	no change	+ 2·3	+ 8·7	+ 2·4	+ 2·7
9	III	V	no	F/T ↑	temporal	no change	**+ 1·7**	+ 7·8	**+ 0·1**	+ 4·0
10	IV	(NA)	no	F/P ↓	none	(NA)	**+ 0·2**	+ 4·1	(NA)	(NA)
11	III	I	good	normal	frontal, temporal	normal	+ 5·4	+ 11·6	+ 2·6	+ 2·6
12	III	I	good	normal	frontal, occipital	no change	+ 3·2	+ 10·3	**+ 1·8**	+ 6·7
13	II	0	good	normal	none	normal	+ 4·4	+ 12·0	**+ 1·0**	+ 3·2
14	II	I	moderate	F/T ↑	none	normal	+ 3·0	+ 10·3	**+ 1·9**	+ 5·1

1) abnormal = deviating more than 2 SD from control mean;
2) clinical function = functional grading before and after shunt operation (see text);
3) cortical rCBF parameters from 9-slice SPECT studies, not available in 3 patients;
4) A/P ratio = significantly increased (↑) or reduced (↓) anterior-posterior ratio of rCBF (F/P, F/T = fronto-parietal, fronto-temporal ratio);
5) cortical regions with significantly increased side-to-side asymmetry (SAI) of rCBF;
6) relative area of subcortical low flow region on SPECT (SC/C) and ventricles on CT (V/C), given in z-scores (deviation from control mean in number of SDs) for the mid-brain slice (slice 4, 5, or 6) with the most abnormal enlargement of ventricles. Normal z-scores (below 2·0) given in bold text.
(NA) = not available

Table 3 Regional cerebral blood flow (rCBF) and side-to-side asymmetry (SAI) of regional cerebral blood flow values measured with SPECT and [^{99m}Tc]-d,l-HMPAO in healthy control subjects and in patients with NPH before and after shunt operation.

ROIs:	Control (N = 14) rCBF		NPH before (N = 11) rCBF		NPH after (N = 9) rCBF	
Cerebral Hemisphere	86·3 (6·6)		80·8 (6·8)		84·4 (9·0)	
Frontal Cortex (F)	85·5 (6·3)		85·1 (5·6)		84·5 (7·3)	
Temporal Cortex (T)	89·3 (6·3)		89·0 (4·0)		92·0 (9·5)	
Superior temporal gyrus and insula cortex (T1)	93·5 (8·5)		97·7 (8·7)		98·9 (11·7)	
Inferior and middle temporal gyrus (T2)	89·1 (6·6)		85·6 (6·7)		90·4 (11·1)	
Temporal poles (T3)	78·1 (7·0)		74·2 (6·6)		75·8 (7·3)	
Parietal Cortex (P)	89·1 (7·3)		93·7 (10·7)		90·4 (11·2)	
Occipital cortex (OC)	103·1 (10·8)		109·9 (11·3)		105·6 (12·3)	
Hippocampus (HC)	83·0 (6·3)		77·0 (11·4)		77·2 (7·7)	
ROIs:	SAI	m|SAI|	SAI	m|SAI|	SAI	m|SAI|
Cerebral Hemisphere	0·8 (2·0)	1·7	0·5 (7·4)	4·9	−2·3 (5·8)	3·9
Frontal Cortex (F)	0·8 (2·8)	2·2	−2·3 (8·1)	5·9	−4·6 (6·5)	5·1
Temporal Cortex (T)	1·8 (3·9)	3·4	1·4 (9·3)	6·8	−0·7 (6·0)	4·8
Superior temporal gyrus and insula cortex (T1)	3·1 (5·1)	5·2	1·0 (7·8)	5·5	0·1 (6·8)	5·3
Inferior and middle temporal gyrus (T2)	1·0 (4·1)	3·3	2·4 (13·4)	10·5*	−1·0 (7·4)	5·8
Temporal poles (T3)	1·1 (6·1)	4·5	0·9 (11·7)	8·5	−1·7 (5·4)	4·7
Parietal Cortex (P)	1·7 (3·3)	2·9	1·2 (5·5)	4·5	0·2 (5·9)	4·2
Occipital cortex (OC)	−0·9 (3·7)	3·1	1·1 (5·3)	4·1	−2·0 (7·1)	4·9
Hippocampus (HC)	−2·3 (6·0)	5·1	−1·5 (11·0)	8·0	−5·7 (7·8)	6·9

The results are presented as mean (SD) for all subjects with a full 9 slice SPECT study. rCBF = regional cerebral blood flow relative to cerebellar blood glow given in %. SAI = side-to-side asymmetry index given in % (see text). A negative value indicates that left rCBF > right rCBF. m|SAI| = mean numerical SAI. Data from the 9 frontal and parietal subregions are not shown, but they were included in the statistical analysis. Data in the NPH group were compared with data from the control group using Wilcoxon two-sample tests (* = $p < 0.002$), and data from before and after shunt operation were compared using Wilcoxon matched-pairs tests. After Bonferroni correction to adjust for multiple comparisons, there were no other significant differences (effective significance level 0·003).

specificity of the Evans' ratio for predicting clinical outcome after shunt operation was 50% and 100%, respectively. There was no significant difference in the cortical atrophy ratings, between the control subjects (median 0, range 0–20) and the NPH patients (median 3, range 0–10). There was a significant reduction, although not complete normalisation, of ventricle size ($p < 0.05$) and Evans' ratio ($p < 0.01$) after shunt operation (table 1).

Global, cortical and subcortical rCBF in patients with NPH vs control subjects

Results are presented as mean (SD) values. Global CBF, as measured with the ^{133}Xe inhalation method, was 62·5 (8·9) ml/(100g·min) and 58·9 (7·7) ml/100g·min) in the NPH and the control groups, respectively (non-significant). No significant differences were seen in the regional CBF data. $FECO_2$ was significantly higher in the NPH group (4·6 (0·6) %) than in the control group [3·9 (0·6) %].

Table 4 Regional cerebral blood flow measured with SPECT and [^{99m}Tc]-d,l-HMPAO in healthy control subjects and in patients with NPH: subcortical low flow region.

	Control (N = 14) Mean (SD)	NPH before (N = 14) Mean (SD)	NPH after (N = 13) Mean (SD)
Relative area of ventricles on CT (V/C %)			
slice 4	3·1 (3·1)	26·4 (10·9)**	17·1 (4·9) +
slice 5	5·1 (2·9)	28·1 (9·9)**	18·6 (8·5) + +
slice 6	6·2 (3·5)	22·2 (6·6)**	16·7 (7·4)
Relative area of central low flow region (%)			
slice 4	23·2 (6·5)	42·2 (12·2)**	31·0 (7·7) +
slice 5	23·2 (7·6)	44·6 (11·5)**	34·0 (11·2) +
slice 6	17·4 (4·4)	38·8 (12·8)**	26·7 (11·1) +

The results are presented as mean (SD). ** = $p < 0.01$ for comparison of NPH vs. control group, Wilcoxon two-sample test. +, + + = $p < 0.05$, $p < 0.01$ for comparison of data before and after shunt operation, Wilcoxon matched-pairs test. The total SPECT slice area measured in number of pixels was 1387 (112), 1563 (98), and 1591 (124) in slice 4, 5, and 6 respectively. There was no significant differences in these figures between NPH and control and between pre- and post-shunt images.

Mean CBF data obtained with the [^{99m}Tc]-*d,l*-HMPAO technique are presented in tables 3 and 4. As in the ^{133}Xe study, there was no significant difference in global CBF or in the regional CBF data. The fronto-parietal ratio of rCBF, however, was significantly lower ($p < 0.05$) in NPH patients (0·92 (0·09)) than in control subjects [0·96 (0·04)], while there was no significant difference in the fronto-temporal ratio. Generally, the mean numerical SAI values were highest in the NPH group (ranging from 4·1% to 11·4% in different ROIs) compared with the control group (ranging from 2·2% to 5·3%). After Bonferroni correction, only the inferior and mid-temporal cortex had a significantly enhanced SAI (table 3).

The mean rCBF of the central white matter (centrum semiovale) was slightly reduced ($p < 0.05$): 51·6 (12·7) % in NPH versus 63·0 (7·5) % in control subjects. The SAI of the central white matter was significantly ($p < 0.05$) higher in NPH (+6·0 (13·0)] %, mean numerical value 11·4%) than in control subjects (−2·3 (5·5) %, mean numerical value 4·9 %). The analysis of the subcortical low flow region is presented in table 4. In slice 4, the mean area of the subcortical low flow region, relative to the total SPECT slice area, was 42·2 (12·2) % in NPH patients and 23·2 (6·5) % in control subjects ($p < 0.01$). Computerised measurement of the area of ventricles on the equivalent CT slice showed that the ventricles occupied in mean 26·4 (10·9) % of the total slice area as opposed to 3·1 (3·1) % in control subjects ($p < 0.01$). Accordingly, NPH was associated with enlarged ventricles, an enlarged subcortical low flow region, and a reduction of the area of the cortical high flow region. Similar results were obtained in slices 5 and 6 (table 4).

The effect of shunt-operation on rCBF

In the NPH group as a whole, no significant post-shunt changes were observed in global or regional cortical CBF. The size of the subcortical low flow region as well as the area of the ventricles were reduced significantly after shunt-operation, although still abnormal (table 4).

rCBE patterns and size of ventricles in individual patients

Before shunt operation. All patients had an abnormal SPECT pattern with enlargement of the subcortical low flow region, focal cortical blood deficits, or both (table 2). The area of the subcortical low flow region was enlarged in 10 of the 14 patients (figs 3–4). In four of these patients (cases 3, 6, 11, and 12) the mean blood flow in the surrounding cortical rim was significantly increased. The ventricles, as measured on the equivalent CT slices, were significantly enlarged in all 14 patients (table 2). Nine of the 11 patients with a full 9-slice HMPAO study had a significantly increased SAI in at least one large cortical ROI or a significantly abnormal anterior-posterior ratio of cortical rCBF (table 2). The flow patterns were heterogenous with posterior as well as frontal flow deficits (figs 3–5). The remaining two patients had normal cortical rCBF. All patients with an enlarged subcortical low flow region had a good or moderate clinical outcome after shunt operation. The four patients with a significantly increased mean flow in the cortical rim had a particularly good clinical outcome. Three of the four patients with a normal subcortical low flow region had a poor clinical outcome. The diagnostic sensitivity and specificity of the area of the subcortical low flow region in predicting surgical outcome was 75% and 100%, respectively. There was no clear correlation between focal cortical blood flow deficits and clinical outcome.

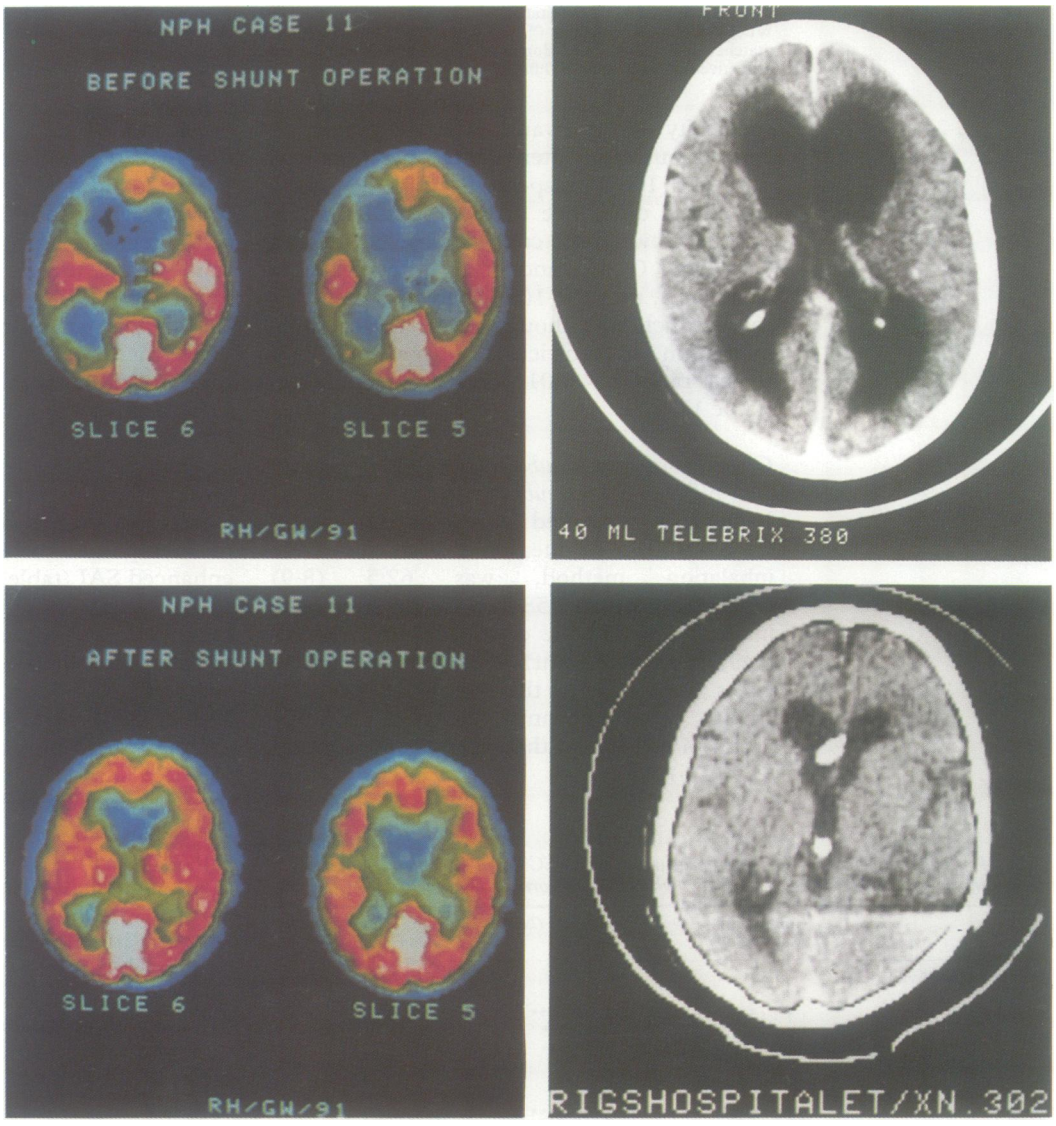

Figure 3 SPECT with [^{99m}Tc]-d,l-HMPAO (left) and CT (right) of the brain in a 72 year old female patient (case 11) with NPH of unknown aetiology before (top) and 3 months after (bottom) shunt operation. The left hemisphere is shown to the left. The colour scale for the SPECT images is shown in fig. 2. However, for the top SPECT image obtained before shunt operation the scale values were higher (0–160%). This patient had a severely enlarged subcortical low flow region. The mean rCBF in the surrounding cortical rim was elevated, despite severe focal flow deficits, particularly in the left frontal and temporal lobes. After shunt operation (with a good clinical outcome), cortical rCBF was normalised, and the area of the subcortical low flow region was markedly reduced, although not normalised.

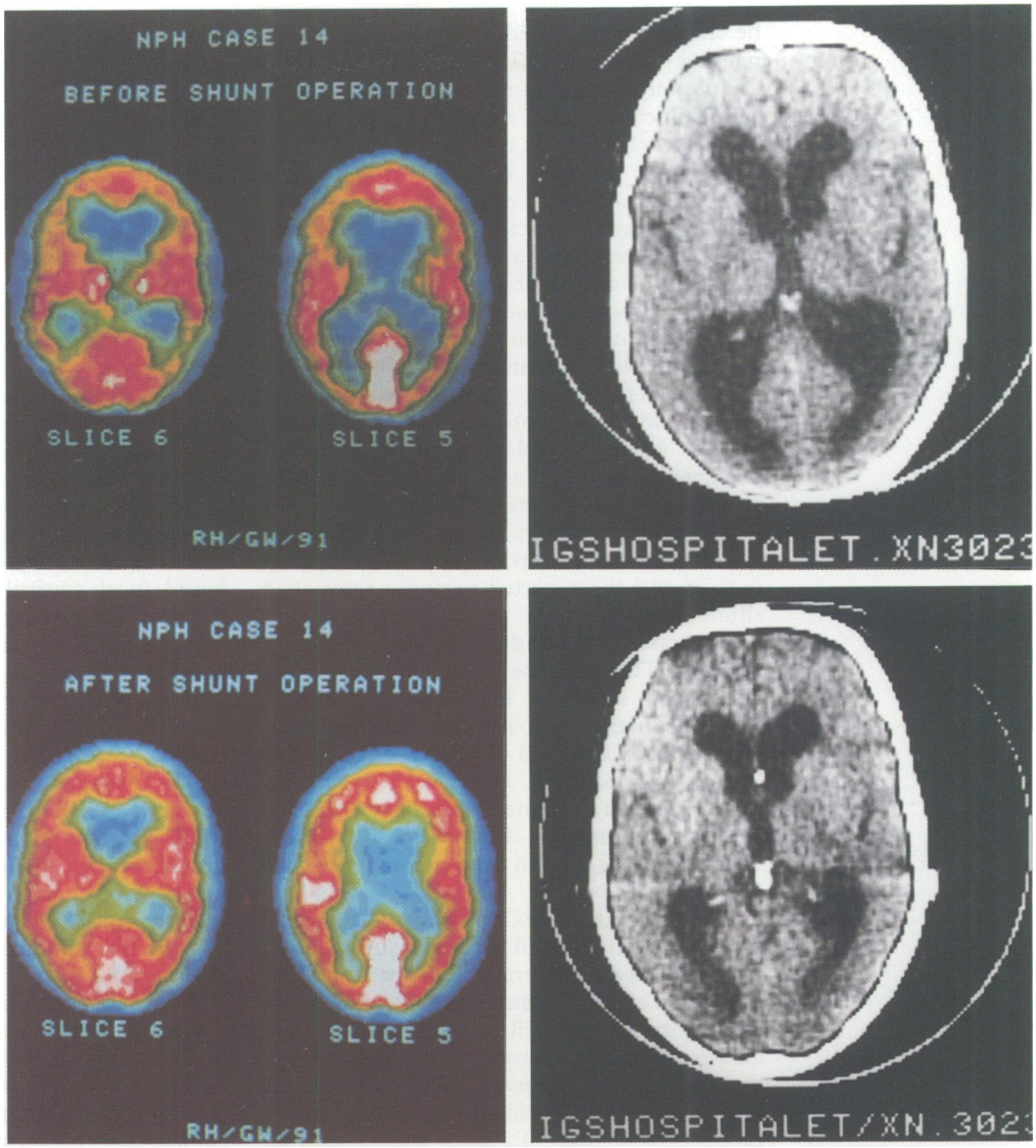

Figure 4 SPECT with [^{99m}Tc]-d,l-HMPAO (left) and CT (right) in a 66 year old male patient (case 14) with NPH, secondary to a head trauma, before (top) and 6 months after (bottom) shunt operation. The left hemisphere is shown to the left. The colour scale for the SPECT images is shown in fig 2. This patient had an enlarged subcortical low flow region and focal cortical blood flow deficits in the temporal cortex. After shunt operation (with a moderate clinical outcome) the rCBF pattern seen on SPECT was normalised.

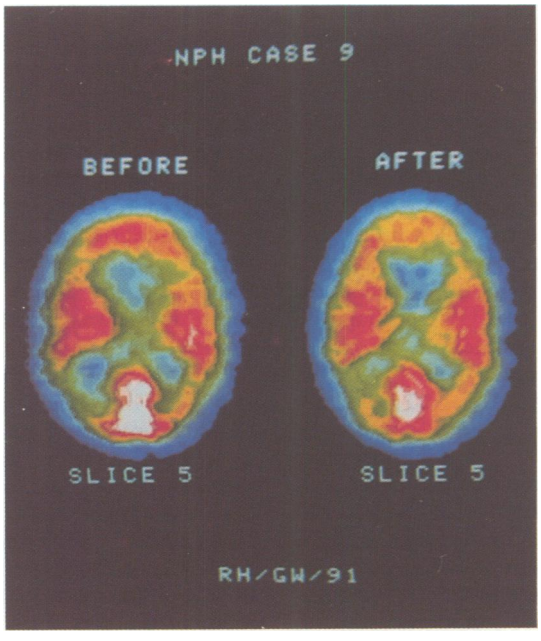

Figure 5 SPECT with [^{99m}Tc]-d,l-HMPAO in a 71 year old male patient (case 9) with NPH of unknown origin before (left) and 4 months after (right) shunt operation. The left hemisphere is shown to the left. The colour scale is shown in fig. 2. This patient had a large, but normal, subcortical low flow region and focal cortical blood flow deficits particularly in the left hemisphere. Despite fulfilling the clinical and hydrodynamic criteria for NPH, this patient had no effect of the operation and deteriorated further. Regional CBF was unchanged.

After shunt operation. In five patients the size of the enlarged subcortical low flow region was normalised (fig 4), in a further four patients it was reduced (fig 3), and in one patient unchanged or slightly greater (table 2). Increased mean cortical blood flow was reduced after shunt in all cases. The midbrain area of the ventricles on CT was normalised in one patient, reduced in 10 patients, unchanged in one patient, and increased in one patient. Cortical blood flow deficits were normalised in three patients and unchanged in four patients. In one of the latter patients (case 8) the frontal flow deficit was related to a small infarct (table 1).

Discussion

Regional cerebral blood flow in NPH

To our knowledge this study is the first to use [^{99m}Tc]-d,l-HMPAO with high resolution SPECT in NPH to measure the area of the subcortical low flow region, a region of primary interest in NPH. Although NPH should

be defined from clinical, CT, and hydrodynamic criteria, SPECT may serve a separate and important role in the differential diagnosis. Clinically NPH may resemble normal ageing, benign senile forgetfulness, Alzheimer's disease, or other degenerative dementia disorders, which may be associated with enlarged ventricles and similar symptoms. The ventricles are larger in NPH than in elderly control subjects, but there is no objective way to absolutely differentiate hydrocephalus from central atrophy. Periventricular white matter hypodensities on CT or hyperintensities on MRI are frequently seen in elderly patients, and also in patients without evidence of dementia.[15] The relative occurrence in NPH and the significance in relation to CSF shunting is questionable.[15-17] Although it has been shown that increased R_{out} is significantly associated with surgical outcome,[4 18] the reported response rates after shunt operation are highly variable, even when taking hydrodynamic criteria into account. The response rate in our study was about the same as in previous studies.[18] SPECT might help identify patients with degenerative dementia disorders, not likely to benefit from surgery. However, it is still an open question, whether Alzheimer's disease or other degenerative diseases could be associated with a partial and reversible CSF absorption defect.

In this study SPECT correctly classified patients from control subjects, in that all patients had an abnormal rCBF pattern. The individual rCBF patterns were heterogeneous with cortical as well as subcortical flow abnormalities. The most frequent pattern was that with an enlargement of the subcortical low flow region associated with focal cortical blood flow deficits. Patients with a normal subcortical low flow region were unlikely to respond clinically to shunt operation.

There are at least three studies of tomographic rCBF using SPECT in NPH.[19-21] Vorstrup *et al*[19] in a study using the ^{133}Xenon inhalation method and SPECT found abnormal preoperative SPECT scans in all 17 patients with either an abnormal large central low flow area or a reduced flow bilaterally in the occipital and contiguous temporo-parietal regions. Postoperative improvement of rCBF was seen in six of the 17 patients. Moretti *et al*[20] used ^{123}I-IAMP with SPECT to study 23 patients with NPH. They found a frontal and parietal hypoactive pattern which improved after shunting in patients with a good clinical outcome. Graff-Radford *et al*[21] studied 22 NPH patients with the ^{133}Xe-inhalation method and found a reduction of global CBF, preferentially affecting the frontal lobe. An anterior/posterior ratio of 1·05, together with the relative duration of B-waves, the duration of dementia, and gait abnormality preceding dementia, correctly classified surgical outcome in a majority of patients.[22] In our patients the anterior/posterior ratio did not determine surgical outcome. As in this study, post-shunt changes in CBF did not accompany improvement in the functional state in all patients.

Brooks *et al*[23] studied regional cerebral oxygen extraction, oxygen metabolism, and CBF, with positron emission tomography in seven patients with NPH, three of whom had idiopathic NPH. The oxygen extraction was normal. The rCBF matched the reduced regional oxygen metabolism. No improvement of rCBF was seen after shunt operation. Jagust *et al*[24] studied regional glucose metabolism with positron emission tomography in 3 patients and found a global reduction of metabolism.

Thus most studies found a global reduction of flow and metabolism, while in our study global CBF, measured with two different methods, was normal. It is likely that with our individualised ROI templates the brain tissue was better delineated from extracerebral structures. Some of the previous studies found focal cortical flow deficits, but there has been disagreement as to their typical location. In this study the analysis of the fronto-parietal ratio and the side-to-side asymmetry ratio of rCBF pointed to a fronto-temporal predilection. In the individual analysis of rCBF, however, it became clear that the rCBF patterns were heterogenous. The observed rCBF patterns differed from the rCBF patterns in other dementia disorders: in Alzheimer's disease a global CBF reduction is seen, but with a disproportionate reduction of rCBF in posterior brain regions. The rCBF patterns are heterogenous and always abnormal, often with severe focal rCBF reductions in fronto-parietal association areas. Severe enlargement of the subcortical low flow area is uncommon.[25] Although no direct comparisons were made, the rCBF pattern in at least one of the patients with no clinical improvement after shunt operation resembled Alzheimer' disease. In frontal lobe dementia[26] and in Huntington's chorea[27] rCBF is reduced primarily in fronto-temporal brain regions. Except for a reduction of rCBF in the caudate nuclei in the latter disease, subcortical blood flow has not been described as abnormal.

The enlargement of the subcortical low flow region which was observed in this study was due primarily to the enlarged ventricles. However, the area of the subcortical low flow region was normal in some of the patients with considerably enlarged ventricles. Furthermore, the subcortical low flow region was normalised after shunt operation even in patients with still very large ventricles. Finally, in the group of NPH patients as a whole there was a reduction of rCBF in the central white matter, probably contributing to the enlargement of the subcortical low flow region. Thus the area of this region on SPECT contained information that was different, and in some ways superior, to that of the size of ventricles on CT. We speculate that enlargement of the ventricles due to NPH leads to a significant, and partly reversible, enlargement of the subcortical low flow region on SPECT. In contrast, enlargement of the ventricles due to central atrophy

may only slightly, or not at all, increase the area of the subcortical low flow region. Cortical blood flow deficits were improved after shunt operation in only a few patients. Probably, the NPH condition had already caused irreversible structural changes with tissue degeneration, or some patients may have had a primary degenerative dementia disorder. Although the Evans' ratio was also associated with surgical outcome, CT data were less successful than SPECT in predicting clinical outcome. However, both CT and SPECT are important tools for defining diseases other than NPH, which could have caused dementia, before the final decision about surgery is made.

Methodological considerations

[^{99m}Tc]-d,l-HMPAO is a lipophilic tracer compound for measurements of rCBF with SPECT. The regional distribution in the brain is proportional to rCBF,[28] although a linearisation correction is preferable to correct for a preferential back-diffusion from high flow regions.[13] The HMPAO method has already proved to be a valuable tool in the focal diagnosis of epilepsy,[29] and in the study of normal ageing[8] and degenerative neuropsychiatric diseases.[25-27 30] Frontal and subcortical regions are visualised particularly well in comparison with the ^{133}Xe inhalation method. The [^{99m}Tc]-*d,l*-HMPAO method, however, does not easily offer quantitative data, as does the ^{133}Xe inhalation method.[8 28] Data obtained with the [^{99m}Tc]-*d,l*-HMPAO method are therefore usually expressed as regional count-rates relative to the mean count-rate of a reference region, in our study, the cerebellum.[8] The cerebellum was chosen as reference region in NPH, because mean rCBF in the cerebellum measured with the ^{133}Xe method, was not different from the control group, and because NPH is not known to be associated with structural abnormalities in the cerebellum. We used the cerebellar hemisphere with the highest blood flow as reference region to avoid cerebellar tissue influenced by any crossed cerebellar diaschisis. However, significant side-to-side asymmetry was not seen in any patient. It is unlikely therefore that global CBF was artefactually raised because of low flow in the cerebellum. The higher $FECO_2$ during the ^{133}Xe study in patients with NPH, compared with healthy control subjects, may have been caused by differences in the degree of hyperventilation during the inhalation procedure. Although this may have added to differences in CBF as measured with the ^{133}Xe method, it could not have significantly affected CBF measured in the [^{99m}Tc]-*d,l*-HMPAO study. The cortical ROIs shown in fig 1 were defined in recognition of the in-plane and axial resolution of the method. They were partly arbitrary and partly based on anatomical landmarks, such as large sulci, easily recognisable on most SPECT images, even in NPH. Because of the disturbed anatomy of the NPH brain and the interindividual variability, the definition of most ROIs could not be based on a stereotactic atlas.

Pathophysiology of NPH

Theoretically, the different abnormal rCBF patterns seen in NPH could reflect several stages of the disease: Initially a progressive resistance to outflow of CSF leads to enlarged ventricles.[3 4] As a result, the area of the subcortical low flow region increases. Later, compromised white matter rCBF and persistent brain dysfunction is caused by continued tension against the brain tissue across the ependymal surface of the ventricles. There is a further increase in the area of the subcortical low flow region, and mean rCBF in the thinned cortical rim increases. After some time, due to deafferentation from the suffering white matter, focal cortical blood flow deficits appear, leaving the mean cortical blood flow subnormal. With further progression of the disease the subcortical low flow region may be extremely large, and severe cortical blood flow deficits appear (fig 3). Even at this point, the SPECT abnormalities may still be reversible after shunt operation.

The relative increase of mean rCBF in the thin cortical rim in some patients was probably caused by a higher proportion of grey matter tissue relative to white matter tissue and a higher neuron density, than in the broader cortical rim of the control subjects. Alternatively, the rise in cortical rCBF could be artefactual and caused by a reduced blood flow in the cerebellum. This is unlikely, as the four patients all had a normal rCBF in the central white matter (relative to the cerebellum). Furthermore, their mean blood flow in the cerebellum measured with the ^{133}Xe technique was within the normal range (in 3 of them even high in the normal range).

The heterogeneity of rCBF patterns could reflect different underlying degenerative or vascular dementia disorders, as already discussed. Patients with a poor or a missing response to shunt operation and periventricular hypodensities on CT could also have suffered from subcortical arteriosclerotic encephalopathy.[17] Only studies with post-mortem analysis or biopsy would clarify this important question.

In conclusion, NPH is associated with an enlargement of the subcortical low flow region, a relative reduction of blood flow in the frontal cortex, and an asymmetrical reduction of rCBF in the inferior and mid-temporal cortex, and in the central white matter. In this study individual rCBF patterns on SPECT were all abnormal, but heterogenous, with the most frequent pattern being an enlarged subcortical low flow region, in some cases associated with focal cortical blood flow deficits. Shunt operation normalised or improved the rCBF pattern in most patients, and improved the clinical status of 11 patients, 10 of whom had a significantly enlarged subcortical low flow region. Three (of 14) patients, all having focal cortical rCBF deficits together with a normal subcortical low flow region, did not improve clinically after shunt operation. We therefore suggest that SPECT may help to identify

patients not likely to benefit from shunt operation, a hypothesis to be tested in a larger sample of patients with more detailed longitudinal neuropsychological evaluation.

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