Original article

Nuclear Medicine Communications

Voxel-based assessment of spinal tap test-induced regional cerebral blood flow changes in normal pressure hydrocephalus

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Objective Normal pressure hydrocephalus (NPH) is a cause of dementia that may be amended by medical intervention. Its diagnosis is therefore of major importance and the establishment of response criteria to cerebrospinal fluid (CSF) shunting is essential. One of these criteria is the clinical response to spinal tap. The accuracy of the spinal tap test could potentially be improved by adding neuroimaging of regional cerebral blood flow (rCBF) changes to the response criteria. Statistical parametric mapping (SPM) is a voxel-based method of image analysis that may be used to statistically assess the significance of rCBF changes. The objective of this study was to evaluate, by SPM, spinal tap test-induced rCBF changes in patients with NPH syndrome.

Methods Forty patients with NPH syndrome underwent hexamethylpropylene amine oxime (HMPAO) brain single photon emission computed tomography (SPECT) before and after a spinal tap test (1-day split-dose protocol). The differences in rCBF between these pairs of scans were analysed by SPM in the whole group and between subgroups divided according to gait improvement at the spinal tap test.

Results In the whole group of patients, there was no statistical difference between pre- and post-spinal tap SPECT images. SPM analysis of patients grouped as a function of their clinical response to the spinal tap test revealed a significant post-spinal tap rCBF increase in the bilateral dorsolateral frontal and left mesiotemporal cortex in clinically responding compared with non-responding patients.

Conclusion According to SPM analysis, gait improvement at the spinal tap test in patients with NPH syndrome is associated with an rCBF increase localized in the bilateral dorsolateral frontal and left mesiotemporal cortex. *Nucl Med Commun* 26:757–763 © 2005 Lippincott Williams & Wilkins.

Nuclear Medicine Communications 2005, **26**:757–763

Keywords: cerebral blood flow, cerebrospinal fluid shunting, dementia, hexamethylpropylene amine oxime, normal pressure hydrocephalus, SPECT, statistical parametric mapping (SPM)

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Received 19 October 2004 **Revised** 28 January 2005
Accepted 29 April 2005

Introduction

The criteria for the diagnosis of normal pressure hydrocephalus (NPH) include progressive gait disturbance, dementia, urinary incontinence or urgency (the Hakim and Adams triad) and ventricles dilated out of proportion to any sulcal enlargement. Decreased cerebral perfusion probably participates in the pathophysiological mechanisms leading to this syndrome. Possible mechanisms for decreased regional cerebral blood flow (rCBF) in NPH include stretching and compression of the intraparenchymal capillaries due to an imbalance between cerebrospinal fluid (CSF) production and resorption [1,2]. Vasomotor influences through reflex constriction of the vessels and stretching of the cholinergic projection fibres of the basal nucleus, with consecutive impairment of the autoregulatory capacity of rCBF, have also been proposed as possible mechanisms for decreased rCBF [1].

Clinically, NPH may resemble normal aging, Alzheimer's disease or other degenerative dementing disorders, which may also be associated with enlarged ventricles. The ventricles are larger in patients with NPH than in elderly control subjects, but overlap is such that NPH diagnosis cannot rely solely on structural changes. The existing diagnostic procedures include magnetic resonance imaging (MRI), computed tomography (CT), clinical assessment before and after spinal tap test, lumbar infusion tests and more invasive tests such as continuous intracerebral pressure measurements. NPH has been shown to be treatable by a CSF shunt [3] and this treatment induces changes in rCBF distribution mainly

characterized by a relative increase in the frontal lobes [1,4–7]. This well-established response to CSF shunting is of major importance, as it places NPH amongst the rare causes of dementia for which curative treatment is achievable.

A good correlation between clinical response to the CSF tap test and outcome after shunt operation has been described previously [8,9], but has not been confirmed by others [10].

Different methods of cerebral perfusion imaging, such as xenon measurements [1,4,11–14], ^{99m}Tc-hexamethylpropylene amine oxime single photon emission computed tomography (^{99m}Tc-HMPAO SPECT) [15], ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT [16] and ^{123}I-isopropyl amphetamine (^{123}I-IAMP) SPECT [6], have shown a positive correlation between increased cerebral blood flow after CSF tap test and clinical improvement after CSF shunting procedures. However, conflicting results have been reported [17,18].

The relative flow pattern obtained by ^{99m}Tc-HMPAO correlates well with that measured by ^{133}Xe [19] and $^{15}CO_2$ positron emission tomography (PET) [20], which makes ^{99m}Tc-HMPAO suitable for imaging rCBF changes.

Until now, semi-quantitative SPECT analysis has usually been based on region of interest (ROI) analysis of elective slices [16,21,22]. A robust approach, such as statistical parametric mapping (SPM), developed at the Wellcome Department of Cognitive Neurology, London, UK [23], evaluates every voxel within the entire brain volume. As the images are normalized to a standard space, SPM also allows precise registration of the observed rCBF changes in the standardized brain coordinate system of Talairach and Tournoux [24]. SPM has previously been validated for clinical PET or SPECT evaluation and has been proven to remove the subjectivity inherent to visual analysis in several neurological conditions [25–33]. Thus, we applied SPM to objectively assess rCBF changes induced in NPH patients by the spinal tap test. The aim of this study was to improve our knowledge about NPH syndrome pathophysiology. We also used SPM to search for a relationship between gait improvement and changes in rCBF distribution after spinal tap.

Patients and methods

Patients

Between January 1999 and September 2002, 40 patients (male to female ratio, 21/19) with presumptive NPH syndrome were included in this study. Their median age was 71 years (range, 36–87 years). Their demographic and clinical data are presented in Table 1.

The diagnosis of presumptive NPH syndrome was based on history, clinical examination and the presence of enlarged ventricles out of proportion to any sulcal enlargement on CT or MRI. The mini-mental state (MMS) score [34] was tested before the spinal tap. As specific neuropsychological tests have been found to be of little value in distinguishing patients with need for a shunt [35], such tests were not performed in our patient group.

Gait disturbance was present in all patients. Twenty patients (50%) showed memory deficit, and 11 patients (27%) had urinary incontinence. In all patients, CT and/or MRI showed communicatory hydrocephalus with an extended ventricular system. Nine of the 40 patients showed significant gait improvement after the spinal tap.

The medical history included infectious meningitis (patient 1), cerebral aneurysm with subarachnoid bleeding (patients 6, 7 and 9), head trauma (patient 12) and brain surgery for meningioma (patient 21), a colloid cyst (patient 32) and both a medulloblastoma and a meningioma (patient 37). One patient had congenital hydrocephalus (patient 5). The other patients had no neurological history. Fourteen patients underwent ventriculo-peritoneal shunt (VPS) placement (Delta Valve, Pudenz-Schulte Medical Corporation, Goleta, California, USA). The decision to perform surgery was made on the basis of a complete clinical work-up, but independent of rCBF. Thirteen of these 14 patients showed clinical improvement after surgery.

Consent for a spinal tap test combined with SPECT examination was obtained from the patient or his/her next of kin. All patients were examined for gait disturbance by an experienced physiotherapist, not aware of the clinical history, before and 2 h and 1 day after spinal tap. For the gait test, the patient had to navigate three times a flat route of 10 m in length; each time, the required number of steps and the duration were recorded. The product of these two values was averaged over the three tests. From these values, we calculated a 'before/after spinal tap' (BAST) ratio, for which the most optimistic value was considered between the 2 h and 1 day post-spinal tap values. Gait improvement was considered to be significant if the BAST ratio was 1.5 (the threshold classically used in routine practice) or higher. The spinal tap test was not feasible in two patients due to insufficient collaboration.

The shunted patients had a clinical follow-up at approximately 3 months after shunt placement.

Brain SPECT

Fresh ^{99m}Tc pertechnetate was eluted from a ^{99}Mo–^{99m}Tc radionuclide generator (Ultra-TechneKow FM, Mallinckrodt

Table 1 Clinical data

Patient/sex/age (years)	History	GD/CD/UI	MMS	BAST ratio	CSF shunt/clinical improvement
1/F/72	Meningitis	+/+/−	26	1.2	Yes/yes
2/F/76		+/+/+	14	ND	No
3/F/67		+/−/+	30	2.2	Yes/no
4/F/72		+/+/+	10	2.1	No
5/M/43	CH	+/−/−	30	≤ 1	No
6/F/65	CA with SAB	+/+/−	23	≤ 1	No
7/M/63	CA with SAB	+/+/+	20	≤ 1	Yes/yes
8/M/73		+/−/−	30	9.4	Yes/yes
9/M/49	CA with SAB	+/+/+	29	≤ 1	No
10/M/70		+/−/−	30	≤ 1	No
11/F/78		+/+/+	21	1.7	Yes/yes
12/F/78	Head trauma	+/+/−	NA	≤ 1	No
13/F/67		+/+/−	30	≤ 1	No
14/M/76		+/−/−	30	1.3	Yes/yes
15/F/85		+/−/−	30	≤ 1	No
16/M/87		+/+/−	25	≤ 1	No
17/M/73		+/+/−	27	≤ 1	No
18/M/78		+/−/−	29	≤ 1	No
19/F/78		+/+/−	24	≤ 1	Yes/yes
20/M/74		+/−/−	29	1.5	Yes/yes
21/M/68	Surgery for Me	+/−/−	30	≤ 1	Yes/yes
22/M/70		+/−/−	30	≤ 1	No
23/M/7		+/−/−	30	≤ 1	No
24/M/78		+/−/−	30	1.8	Yes/yes
25/M/72		+/+/+	15	ND	No
26/F/66		+/−/−	15	2.1	Yes/yes
27/F/65		+/+/−	29	≤ 1	No
28/M/66		+/−/−	29	≤ 1	No
29/F/77		+/−/+	NA	≤ 1	No
30/F/73		+/−/+	25	1.3	Yes/yes
31/F/86		+/+/−	11	≤ 1	No
32/M/67	Surgery for CC	+/+/+	NA	1.7	Yes/yes
33/M/68		+/+/+	14	1.5	Yes/yes
34/M/76		+/−/−	26	≤ 1	No
35/M/64		+/+/−	NA	≤ 1	No
36/F/72		+/−/−	29	≤ 1	No
37/F/36	Surgery for MB + Me	+/−/−	30	≤ 1	No
38/F/62		+/+/−	26	≤ 1	No
39/M/81		+/+/−	16	≤ 1	No
40/F/77		+/−/−	30	≤ 1	No

BAST ratio, before/after spinal tap ratio (see text); CA, cerebral aneurysm; CC, colloid cyst; CD, cognitive deficit; CH, congenital hydrocephalus; CSF, cerebrospinal fluid; GD, gait disturbance; MB, medulloblastoma; Me, meningioma; MMS, mini-mental state score; NA, not available; ND, not done; SAB, subarachnoid bleeding; UI, urinary incontinence.

Inc., St Louis, Missouri, USA) and mixed with D,L-HMPAO (exametazime; Ceretec, Amersham, Little Chalfont, Buckinghamshire, UK).

Brain SPECT scans were obtained before (SPECTb) and after (SPECTa) a spinal tap. All scans were obtained parallel to the cantho-meatal plane.

The patient was placed in a quiet, dimly lit room, and was instructed to keep his/her eyes closed. Twenty minutes after the introduction of an intravenous catheter, a bolus of 555 MBq of ^{99m}Tc-HMPAO was injected. SPECTb was obtained 30 min post-injection with a single-headed camera (DSX Rectangular, SMV International, Buc, France) fitted with an ultra-high-resolution collimator, with 64 projections over 360°, 20 s per projection, in a 128 × 128 matrix, and with an axial pixel resolution of 8 mm full width at half-maximum (FWHM). After the acquisition, the patient underwent a spinal tap with minimum CSF removal of 30 cm^3. Between 1.5 and 2 h after the spinal tap, SPECTa was performed in the same conditions as SPECTb, except that the dose was 1110 MBq and the time per projection was 12 s.

SPECT images (transaxial, coronal and sagittal sections) were reconstructed by filtered backprojection with a modified Shepp-Logan filter (without threshold or zoom) using the camera manufacturer's software.

Statistical analysis

The SPECT data were analysed for spinal tap-induced rCBF changes using SPM99 in a Matlab environment (The Mathworks Inc., Sherborn, Massachusetts, USA). This software was run on a SUN Ultraspark ULTRA 60 workstation (Sun Microsystems Inc., Santa Clara, California, USA). After conversion into an Analyze format (Analyze 4.0, BIR, Mayo Clinic, Rochester, Minnesota, USA), the images were spatially normalized to the generic SPM99 SPECT template. This template approximates the brain space defined by Talairach and Tournoux

[24]. The spatial normalization uses a least-squares approach to match each image volume to the template by a 12-parameter (linear) affine transformation. The normalized images were smoothed with an isotropic Gaussian filter (20 mm FWHM) to increase the signal-to-noise ratio. The image intensity was normalized between subjects by a proportional scaling in order to compensate for variability in global cerebral tracer uptake and for intra-subject variability in injected activity. The analysis used linear contrasts to identify brain regions in which rCBF significantly differed between SPECTa and SPECTb and between the analysed subgroups (interaction analysis). The second cumulative image was considered as the test image. As discussed elsewhere [36], this avoids the increased noise induced by subtraction of the baseline residual activity. In the absence of strong mental activity, in the single-day split-dose procedure, the only significant differences between baseline and test conditions are due to the experimental effect.

The general linear model was used to perform univariate statistical tests at each voxel and to describe the variability in the data in terms of experimental effects and residual variability. This analysis produced a t statistic for each voxel as specified by the contrast, which constituted the statistical parametric map $SPM_{\{t\}}$. The statistical parametric maps for comparison of rCBFa and rCBFb were thresholded at the default probability of $P \leq 0.005$ uncorrected. Data were consecutively analysed for spinal tap-induced rCBF increase (contrast $-1\ 1\ 1\ -1$) as well as decrease (contrast $1\ -1\ -1\ 1$) in the same experimental design. The resulting clusters of voxels were then described in terms of spatial extent and peak height.

Previous studies have revealed a spinal tap- or shunting-induced rCBF increase, most frequently in the frontal and temporal regions [1,4–7,11]. The frontal rCBF change is in line with the fact that all three elements of the Hakim and Adams triad could be explained by a frontal lobe deficit [37]. Based on this a priori knowledge, an anatomically constrained hypothesis about effects in frontal and temporal regions was applied using a small volume correction (spherical volume, diameter 20 mm). Regions were interpreted and reported as significant in all group and individual analyses if they contained voxels with $P_{\text{corrected}} \leq 0.05$. These areas were displayed as maximum intensity projections on a glass brain in the three orthogonal projections.

Results

Substantial improvement after shunting occurs in about 30–50% of idiopathic and 50–70% of secondary NPH cases [38]. In our series, clinical improvement was observed in 13 of the 14 shunted patients (93%). Nine of the 10 patients with primary NPH and all four of the patients with secondary hydrocephalus improved after shunting.

There were no clusters with significant rCBF changes between SPECTa and SPECTb when the group was analysed as a whole.

When comparing the patients with an MMS score of ≤ 25 ($n = 13$) with those with an MMS score of > 25 ($n = 23$), no clusters of significant rCBF difference were detected.

Patients were divided into two groups according to their clinical response to the spinal tap: group 1, BAST ratio of ≥ 1.5 ($n = 9$); group 2, BAST ratio of < 1.5 ($n = 29$). Eight patients in group 1 underwent VPS surgery and seven of these showed clinical improvement (subgroup 1a). The six patients in group 2 who had VPS placement showed a favourable clinical response. In group 1, a significant increase in rCBF after spinal tap was observed in the middle gyrus of the frontal lobes and in the parahippocampal gyrus of the left temporal lobe, compared with patients in group 2 in whom a slight decrease may have occurred ($P_{\text{corrected}}$ at the voxel level < 0.05; Figs. 1 and 2). The coordinates and localization of the voxels with the lowest P value of each cluster are shown in Table 2. Comparison based on the BAST ratio response in improved patients (contrast between subgroup 1a and group 2) revealed no significant difference in rCBF change after spinal tap. Analysis of the spinal tap-induced rCBF change in each individual of group 1 compared with all patients in group 2 revealed no individual differences, except in patient 11, a patient with the complete clinical triad, in whom a significant rCBF increase ($P < 0.05$) was observed in the right gyrus fusiformis. The limited variation of the BAST ratio made this variable unsuitable for use as a covariate.

Discussion

In the present study, a voxel-by-voxel approach was applied to HMPAO brain perfusion SPECT analysis in order to detect significant rCBF changes induced by a spinal tap test in NPH syndrome. We found that the

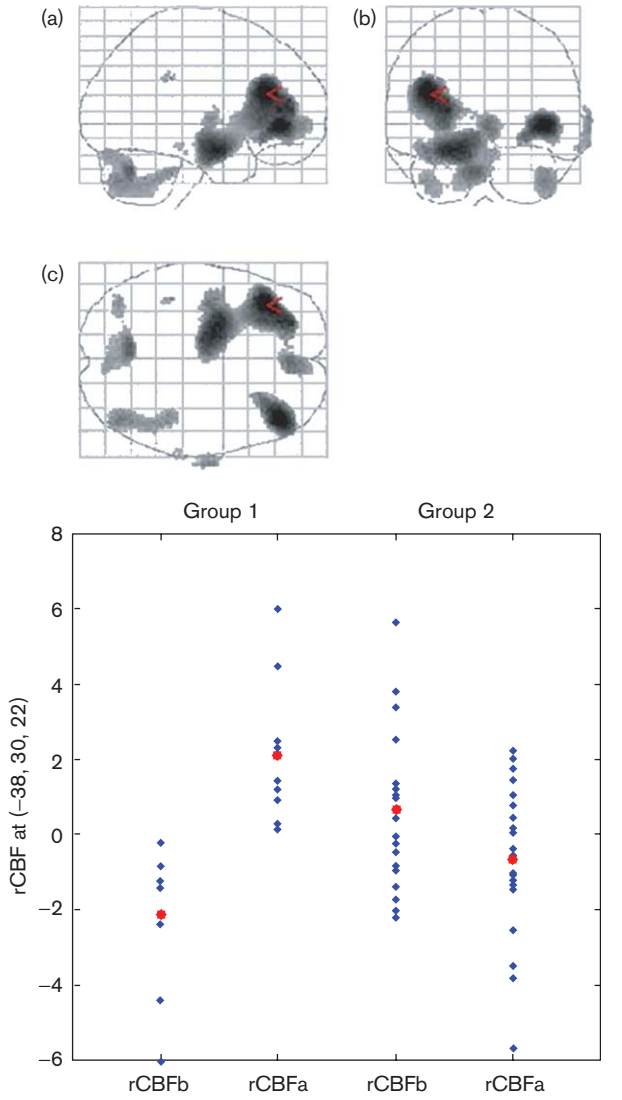
Table 2 Statistical parametric mapping (SPM) analysis on single photon emission computed tomography (SPECT) data

Coordinates* (x, y, z) (mm)	Localization	$P_{\text{corrected}}$ (k,Z)
−38, 30, 22	Left middle frontal gyrus	0.018 (1533, 3.68)
42, 42, −2	Right middle frontal gyrus	0.015 (874, 3.72)
−20, −6, −18	Left parahippocampal gyrus	0.028 (901, 3.53)

BAST ratio, before/after spinal tap ratio; k, cluster size in voxels; P, cluster level significance; SPECTa, SPECT after spinal tap; SPECTb, SPECT before spinal tap (see text); Z, voxel level Z score. Location of the voxels according to the atlas of Talairach and Tournoux [24].

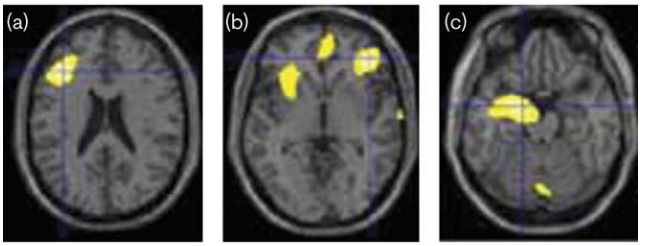
*Coordinates of the voxels with the lowest P value of each cluster according to SPM analysis of patients with a BAST ratio of ≥ 1.5 vs. patients with a BAST ratio of < 1.5, two conditions, SPECTa vs. SPECTb, contrast $-1\ 1\ 1\ -1$.

Fig. 1



Top: clusters of regional cerebral blood flow (rCBF) increase in patients with improved gait after cerebrospinal fluid (CSF) removal (group 1) compared with patients with no gait improvement (group 2), projected onto a glass brain ($P_{corrected}$ at the voxel level < 0.05; a, view from the right; b, view from behind; c, view from the top). An arrowhead indicates the voxel with the most important rCBF increase within the significant cluster of the left middle frontal gyrus (with small volume correction). A symmetric cluster of significant increase is found in the right hemisphere. A significant cluster is also present in the parahippocampal gyrus of the left temporal lobe. Bottom: plot of rCBF change in the specified voxel of the left middle frontal gyrus in groups 1 and 2. Values are centred on group means, marked with a red dot (rCBFb, rCBF before spinal tap; rCBFa, rCBF after spinal tap).

Fig. 2



Areas of regional cerebral blood flow (rCBF) increase after cerebrospinal fluid (CSF) removal in patients with gait improvement at spinal tap test compared with patients with no gait improvement, projected onto the corresponding slices of a normal subject's magnetic resonance image seen from above ($P_{corrected}$ at the voxel level < 0.05). Significant rCBF increase in group 1 is observed in the dorsolateral cortex of the left frontal lobe (a), the right frontal lobe (b) and in the parahippocampal gyrus of the left temporal lobe (c).

spinal tap test induces an rCBF increase in the frontal lobes and in the left mesiotemporal region in patients in whom spinal tap is followed by significant gait improvement, compared with patients with no gait improvement.

As CSF shunting is a procedure with a non-negligible morbidity (haemorrhage, infection) and mortality, there is a need for reliable tests for diagnosis and for the prediction of response to CSF shunting. Saline infusion with pressure monitoring has been used to demonstrate decreased CSF absorptive capacity. CSF absorptive capacity is quantified as conductance to outflow of CSF (in millilitre uptake of CSF per minute per millimetre of Hg). As yet, there is no clear cut-off level of conductance that would lead to an acceptable accuracy of the test for the prediction of response to a shunting procedure. The measure of conductance to outflow of CSF thus remains of questionable value. Moreover, lumbar infusion tests are rather invasive and involve a risk of infection.

Clinical assessment before and after spinal tap for the evaluation of possible benefits from ventriculo-atrial or ventriculo-peritoneal shunting is most commonly used at present, and usually concentrates on gait modification. Indeed, performance of cognitive tasks is not changed by CSF removal according to several authors, or has been found to be of little value [10,35,39,40].

Considering the difficulties in the clinical assessment of NPH, several authors have attempted to apply functional brain imaging to diagnose amendable NPH. Early isotopic studies on NPH have used planar acquisition with single photon emitters, a technique that is obviously less precise than tomographic evaluation. Traditionally, in SPECT studies, a few transverse slices are selected for quantification [6,12,21,22], leading to undersampling of the brain data. The use of a limited number of ROIs enhances the risk of low reproducibility. A region of reference is often used, e.g. in the occipital cortex [6], the cerebellum [5,6,15,21] or in broader posterior regions [12,22], assuming that no rCBF changes occur in these regions. A common feature of most of these studies is the involvement of the frontal lobes in rCBF changes related to NPH syndrome. Kristensen *et al.* [21] depicted a

widespread rCBF hypoperfusion pattern, with a caudal frontal and temporal grey matter and subcortical white matter reduction of rCBF as the dominant feature. Moretti *et al.* [6] found frontal hypoactivity in the majority of patients. Recently, Hertel *et al.* [16] reported that the combination of the spinal tap test with cerebral perfusion measurement, assessed by either ^{99m}Tc-bicisate SPECT or perfusion-weighted MRI, leads to a better preoperative selection for shunting in suspected idiopathic NPH. The authors found an excellent correlation between SPECT and perfusion-weighted MRI.

Compared with patients without gait improvement, we found rCBF increases in both frontal lobes and in the left temporal lobe in patients with improved gait after spinal tap. The increase in frontal rCBF is most likely due to release of the stretched anterior cerebral arteries and veins by CSF drainage from the enlarged ventricles. This effect is in accordance with the frontal lobe rCBF increase detected after shunting in most previous SPECT studies [1,4–7]. Functional recovery of these areas may explain the improvement in gait, incontinence and cognitive functions, such as those related to judgment and insight, attributable to frontal lobe activity. Stretching of cholinergic fibre connections from the nucleus basalis and enlargement of the temporal horns finally result in impaired perfusion of the temporal regions. This, in turn, may account for memory impairment in NPH. Interestingly, in the left parahippocampal gyrus, a structure that is known to play a critical role in memory, we observed, after spinal tap, a significant increase in rCBF in patients with improved gait compared with patients with no improvement. In one patient, a significant increase in rCBF was present in the left gyrus fusiformis, a region involved in face recognition. This apparently anecdotal observation gains some substance in light of the disability in face recognition reported in children with hydrocephalus [41].

In our image processing, no warping was applied. We therefore cannot totally exclude that the normalization process may have been influenced by a change in the global brain volume after the spinal tap, and may therefore have had some impact on the results obtained. Although changes in the shape of the cortex might be expected due to CSF removal, neither the regional localization, shape nor size of the clusters with rCBF increase suggests that they would be caused by structural modifications.

At this stage, surgical decision cannot be based on the imaging technique described here, as it does not detect rCBF changes in the majority of the individual analyses. The construction of a larger database, ideally within a multicentric network, as available for ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET diagnosis of Alzheimer's disease [42], would certainly increase the power of the individual analyses and perhaps lead to an accurate detection of treatable NPH by SPECT. In the same way, the use of imaging techniques with less variability, such as perfusion-weighted MRI or PET with ^{18}F-FDG or ^{15}O-H_2O, could possibly make neuroimaging of the spinal tap response a valuable add-on for the selection of candidates for efficient surgical CSF shunting amongst patients with suspected NPH.

Conclusion

According to an SPM approach, gait improvement at the spinal tap test in NPH patients is associated with an rCBF increase in the middle gyrus of the frontal lobes and in the parahippocampal gyrus of the left temporal lobe. SPM analysis of rCBF changes in suspected NPH deserves further development in order to provide an objective tool that may help in the management of this condition.

Acknowledgements

This work was financially supported by the Loterie Nationale and the Fonds National de la Recherche Scientifique, Belgium.

The authors thank Xavier De Tiège, Sandra Elincx, Olivier Firket, Koen Van Laere and Gaëtan Van Simaeys for their technical and intellectual help.

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