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The influence of lumbar spinal drainage on diffusion parameters in patients with suspected normal pressure hydrocephalus using 3T MRI

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Abstract

Background: Normal pressure hydrocephalus (NPH) has been an ongoing and challenging field of research for the past decades because two main issues are still not fully understood: the pathophysiologic mechanisms underlying ventricular enlargement and prediction of outcome after surgery.

Purpose: To evaluate changes in diffusion tensor imaging (DTI) derived parameters in patients with suspected normal pressure hydrocephalus before and after withdrawal of cerebrospinal fluid (CSF).

Material and Methods: Twenty-four consecutive patients with clinical and radiological suspicion of NPH and 14 age-matched control subjects were examined with DTI on a clinical 3T scanner. Patients were examined before and 6–36 h after CSF drainage (interval between scans, 5 days). Fifteen patients were finally included in data analysis. Fractional anisotropy (FA) and mean, parallel, and radial diffusivity (MD, PD, RD) were evaluated using a combination of a ROI-based approach and a whole-brain voxel-by-voxel analysis.

Results: Alteration of DTI parameters in patients with suspected NPH is regionally different. Compared to the control group, we found an elevation of FA in the subcortical white matter (SCWM) and corpus callosum, whereas the other diffusion parameters showed an increase throughout the brain in variable extent. We also found a slight normalization of RD in the SCWM in patients after lumbar drainage.

Conclusion: Our results show that DWI parameters are regionally dependent and reflect multifactorial (patho-) physiological mechanisms, which need to be interpreted carefully. It seems that improvement of gait is caused by a decrease of interstitial water deposition in the SCWM.

Keywords

Normal pressure hydrocephalus, magnetic resonance imaging (MRI), diffusion tensor imaging, cerebrospinal fluid (CSF), spinal drainage, tap test, voxel-based analysis

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Introduction

Described first in 1965 by Hakim et al., idiopathic normal pressure hydrocephalus (iNPH) is characterized by the clinical triad of gait disturbance, dementia, and urinary incontinence in patients with enlarged ventricles but mostly normal opening pressure of cerebrospinal fluid (CSF) (1). The underlying pathophysiology is still not fully understood although intermittently increased CSF pressure waves and abnormal CSF flow patterns in the mesencephalic aqueduct were found with different diagnostic modalities (2–4).

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Reliable diagnostic criteria for iNPH and reliable parameters predicting a favorable surgical outcome are lacking (3), partially explaining the considerable variability of the reported success rates between 30% and 96% after ventriculo-peritoneal shunt in long-term follow-up examinations (5). Supplemental tests such as CSF withdrawal (spinal tap test) or long-term monitoring of intracranial pressure (ICP) may increase the predictability moderately (6).

There has been quite some research on magnetic resonance imaging (MRI) in patients with iNPH, mainly focusing on evaluation of CSF flow dynamics in the cerebral aqueduct, proton magnetic resonance spectroscopy, and more recently on diffusion tensor imaging (DTI) of white matter (7,8). DTI is currently widely applied to assess properties of white matter, and noninvasively estimates the amount and direction of water diffusion in the investigated tissue. DTI describes the local diffusion as an ellipsoid using a tensor model (9). In normal white matter, the diffusivity of water molecules is up to four-fold higher in the parallel than in the perpendicular direction in relation to a given fiber tract orientation, causing diffusion anisotropy. Therefore, changes of white matter can be described by parameters of diffusion anisotropy as fractional anisotropy (FA), parallel diffusivity (PD), and radial diffusivity (RD).

A number of recent studies attempted to elucidate the value of DTI for the evaluation of hydrocephalus, either by comparison of patients with healthy control subjects or by intra-individual comparison before and after implantation of a ventriculo-peritoneal shunt (5,10,11). Most of these studies focused on the analysis of FA and MD, disregarding the underlying components PD and RD, with one exception (12). To our knowledge there is no previous study targeting at short-term changes in suspected adult iNPH in a standard time frame before and after spinal CSF withdrawal test with a combination of both region-of-interest (ROI) analysis and whole-brain voxel-based analysis of the FA, MD, PD, and RD at 3T.

Material and Methods

Study population

Thirty-eight subjects participated in this study: 24 consecutive patients (age, 74.9 ± 5.3 years) with clinically suspected chronic iNPH fulfilling the criteria for possible or probable iNPH, and 14 controls. The diagnosis of chronic iNPH was based on the convergent evidence from the clinical history, physical examination, and brain imaging according to the guidelines of Marmarou et al. (13). All patients showed moderate ventricular enlargement (Evans' index exceeding 0.3) and had no identifiable neurologic, psychiatric, or general medical conditions sufficient to explain the presented symptoms otherwise. Nine patients were excluded due to revocation of the patient's consent ($n = 4$), failure of lumbar puncture ($n = 2$), nosocomial pneumonia ($n = 1$), intracerebral hemorrhage due to the intra-cranial pressure (ICP) probe ($n = 1$), and the ICP probe already being applied before MRI examination ($n = 1$). Therefore, 15 patients with suspected chronic iNPH were included in image interpretation and data analysis.

Fourteen age-matched control subjects (age, 74.5 ± 6.6 years) were identified as neurologically normal by review of medical history and neurological examination. Written informed consent to participate in the study was obtained from all subjects.

Study design

The local ethics committee approved this study. All patients underwent extensive clinical testing to assess their benefit from a shunt operation (3) including spinal CSF withdrawal test, long-term measurement of ICP and neurological testing (Table 1). All patients were subject to MRI before and after the clinical testing (time interval of MRI examinations, 5.0 ± 0.7 days). The imaging protocol included T2-weighted sequences and DTI as described in detail below. The control subjects were examined with the identical MRI protocol.

The subsequent evaluation comprised the following three groups: (i) patients before *versus* after CSF tap test; (ii) patients before CSF tap test *versus* controls; and (iii) patients after CSF tap test *versus* controls.

Imaging protocol

MRI was performed on a 3.0 T Magnetom Trio (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel head coil. The anterior and posterior commissure (AC, PC) as well as the AC-PC line were determined with a T2-weighted sequence in sagittal orientation. Subsequent imaging was aligned parallel to the AC-PC line and consisted of a DTI sequence (single-shot echo-planar imaging sequence; TR/TE, 2700/93 ms; field of view [FOV], 230×230 mm; matrix size, 128×128; slice thickness, 5 mm; 20 non-colinear directions; b-value, 1000 s/mm^2; number of averages, 4) and a T2-weighted 3D-sequence (turbo spin-echo; TR/TE, 750/130 ms; echo train length, 21; slice thickness, 1 mm; FOV, 170×200 mm; matrix size, 320×268).

DTI processing

DTI images were converted to NIfTI format using dcm2nii (14). For further preprocessing of the DTI

Table 1. The difference of the Evans' index between patients and control subjects was statistically significant ($P < 0.0001$).

	Patients ($n = 15$)	Control subjects ($n = 14$)	
Age ± SD (years)	72.7 ± 5.1	73.3 ± 6.7	n.s.
Sex	7 women, 8 men	6 women, 8 men	n.s.
Evans' index	0.38 ± 0.05	0.29 ± 0.04	***
mRS	2.86 ± 1.23	n.e.	
S&L	2.29 ± 1.14	n.e.	
MMST	23 ± 4.13	n.e.	
ICP (mm Hg)	8.40 ± 3.5	n.a.	
Drainage (h)	73 ± 19.1	n.a.	
Drainage (mL)	567 ± 211.5	n.a.	
Improvement after tap test	8/15	n.a.	
Shunt implanted	7/15	n.a.	

One patient refused implantation of a ventriculo-peritoneal shunt despite clinical results suggestive of NPH.
ICP, mean intracranial pressure; MMST, Mini-Mental Status Test; mRS, modified Ranking Scale; n.a., not applicable; n.e., not evaluated; n.s., not significant; S&L, Stein & Langfitt scale.

raw data the software package FSL (FMRIB Software Library, www.fmrib.co.ac.uk/fsl) was used (15). The brain extraction tool (16) was applied to remove non-brain tissue and to obtain "brain-only" data. Subsequently the FMRIB's diffusion toolbox was applied to correct distortions caused by eddy currents. FA, MD, and eigenvalue maps were calculated by fitting a tensor model to the raw diffusion data (17). PD was defined as the highest, e.g. 1st eigenvalue of the diffusion tensor. RD was calculated as the mean of the 2nd and 3rd eigenvalue.

Evaluation of the FA, MD, PD, and RD maps between the study groups was done using two different, independent approaches: (i) comparison of manually defined ROI; and (ii) whole-brain voxel-based analysis using Tract-Based Spatial Statistics (TBSS, part of the FSL package) (18). We applied the two methods to cross-validate our findings by minimizing bias due to subjective influences (a potential drawback of the ROI method) or incorrect co-registration algorithms (a potential drawback of the TBSS method) (5).

For the ROI method a combination of the b0-images and the FA maps was used to define regions of interest in exactly defined areas of white matter and subcortical grey matter. Areas were selected based on their close relation to the ventricles indicating involvement in the disease, and their significance for motor and cognitive functions (19). Along the corticospinal tract (CST) of both hemispheres ROI were drawn in the subcortical white matter (SCWM), the periventricular white matter (PVWM), the posterior limb of the internal capsule (PLIC), and the midbrain (MIDB). Along the corpus callosum ROI were placed in the genu (GENU), the body (CCBO), and the splenium (SPLE). ROI were also drawn in the caudate nucleus heads (CAUD), as recent work showed a marked elevation of the FA in chronic hydrocephalus with improvement after shunt surgery (20). Therefore, we obtained 13 different ROI (Fig. 1 shows an example of ROI placement). After drawing the ROI using FSLview (part of the FSL package), they were superimposed as masks on the FA, MD, PD, and RD maps, and the mean values of the ROI were calculated. Bilateral ROIs in the SCWM, PVWM, PLIC, and MIDB were averaged. For statistical group comparison the non-parametric Kruskal-Wallis test was used to test for an overall difference between groups with Dunn's multiple comparison correction for the post-hoc tests between groups. A P value ≤ 0.05 was considered as being significant for all tests.

The TBSS steps and procedures were described in detail by Smith et al. (21). To shortly summarize: All subjects' FA images were aligned to every other one to identify the most representative one and to use this as the target image. This target was then affine-aligned into MNI152 standard space, and every image was transformed into $1 \times 1 \times 1$ mm MNI152 space by combining the non-linear transformation to the target FA image with the affine transformation from that target to MNI152 space. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics using a permutation-based method with a threshold-free cluster detection enhancement implemented in the tool RANDOMISE of FSL (22). The registration warp fields and projection information derived from the FA analysis are then applied

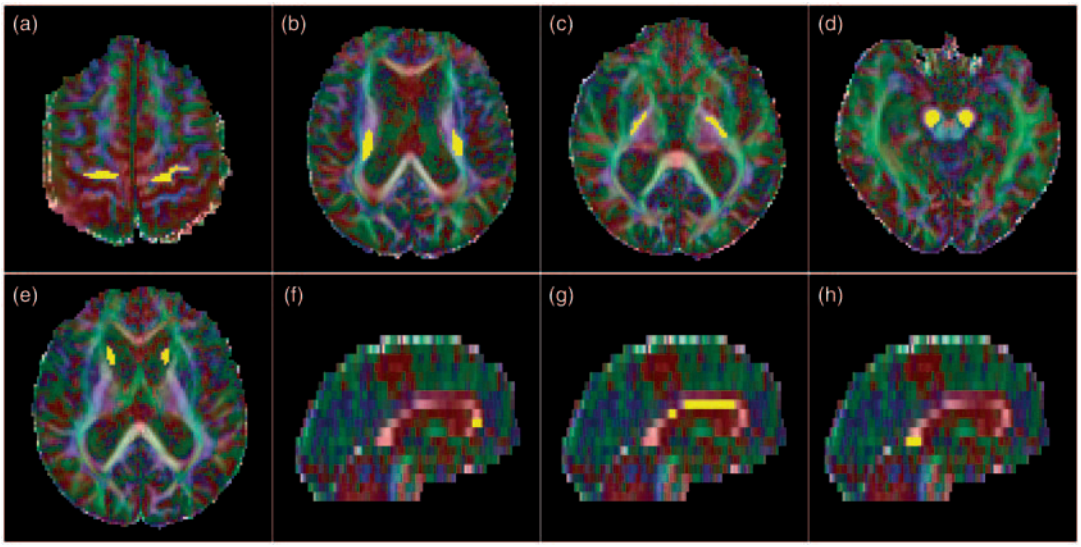

Fig. 1. Placement of the regions of interest in the subcortical white matter (a), the periventricular white matter (b), the posterior limb of the internal capsule (c), the midbrain (d), the head of the caudate nucleus (e), and the corpus callosum: genu (f), body (g), and splenium (h).

to the MD, PD, and RD maps of each subject, ensuring an exact spatial correspondence of the different parameters.

Results

ROI analysis

For the CST, we found significantly lower FA values in patients with iNPH before and also after CSF withdrawal test compared to the healthy control group in the SCWM, and slightly elevated FA values in the PVWM and MIDB. MD, PD, and RD values were overall elevated in patients before and after CSF withdrawal test compared to the healthy control group with variable extent: A significant increase was found in all ROI of the CST for MD; in the PVWM, PLIC, and MIDB for PD; and in the SCWM and PVWM for RD. Furthermore, we found a slight elevation of the RD values in the SCWM before tap-test compared to the measurements after tap-test ($P = 0.046$), as the only significant result in group (1). Fig. 2 displays the results of our ROI analysis for the selected sections of the CST.

In the corpus callosum we found a decrease of the FA values in the iNPH group before and after the CSF withdrawal test, especially in the splenium and to a lesser extent in the body, driven by a simultaneous increase of mainly RD but also PD values, resulting in an increase of MD. In the genu, we observed a minimal increase of the PD in patients after CSF withdrawal test compared to the healthy control group. MD, PD, and RD values showed a significant increase in the caudate nucleus compared to the control group (Fig. 3). For the corpus callosum we did not find significant changes of diffusion parameters before and after CSF withdrawal test.

TBSS analysis

The TBSS results (Fig. 4) confirm the results of the ROI analysis in most regions. MD in patients with iNPH is increased throughout the whole analyzed white matter volume. The FA was significantly decreased in voxels located in the SCWM and the corpus callosum. The analysis of PD and RD showed a widespread increase, mostly of PD, in voxels representing the corpus callosum, corresponding to the decrease of FA. RD increase predominated the PD increase in the SCWM, also corresponding to the decrease of FA. The comparison of patients before and after tap-test showed no significant differences (data not shown).

Discussion

We examined, by means of DTI, microstructural changes of white and deep gray matter in proximity to the lateral ventricles and along the corticospinal tract in patients with chronic iNPH before and after CSF withdrawal test. The analysis of data comprised two complementary approaches, a ROI-based and a whole-brain voxelwise evaluation. Our results show an increase of MD values throughout the white matter in patients with suspected iNPH whereas FA changes were found to be more heterogeneous.

Compared to the control group, we found a significantly decreased FA in the subcortical white matter of

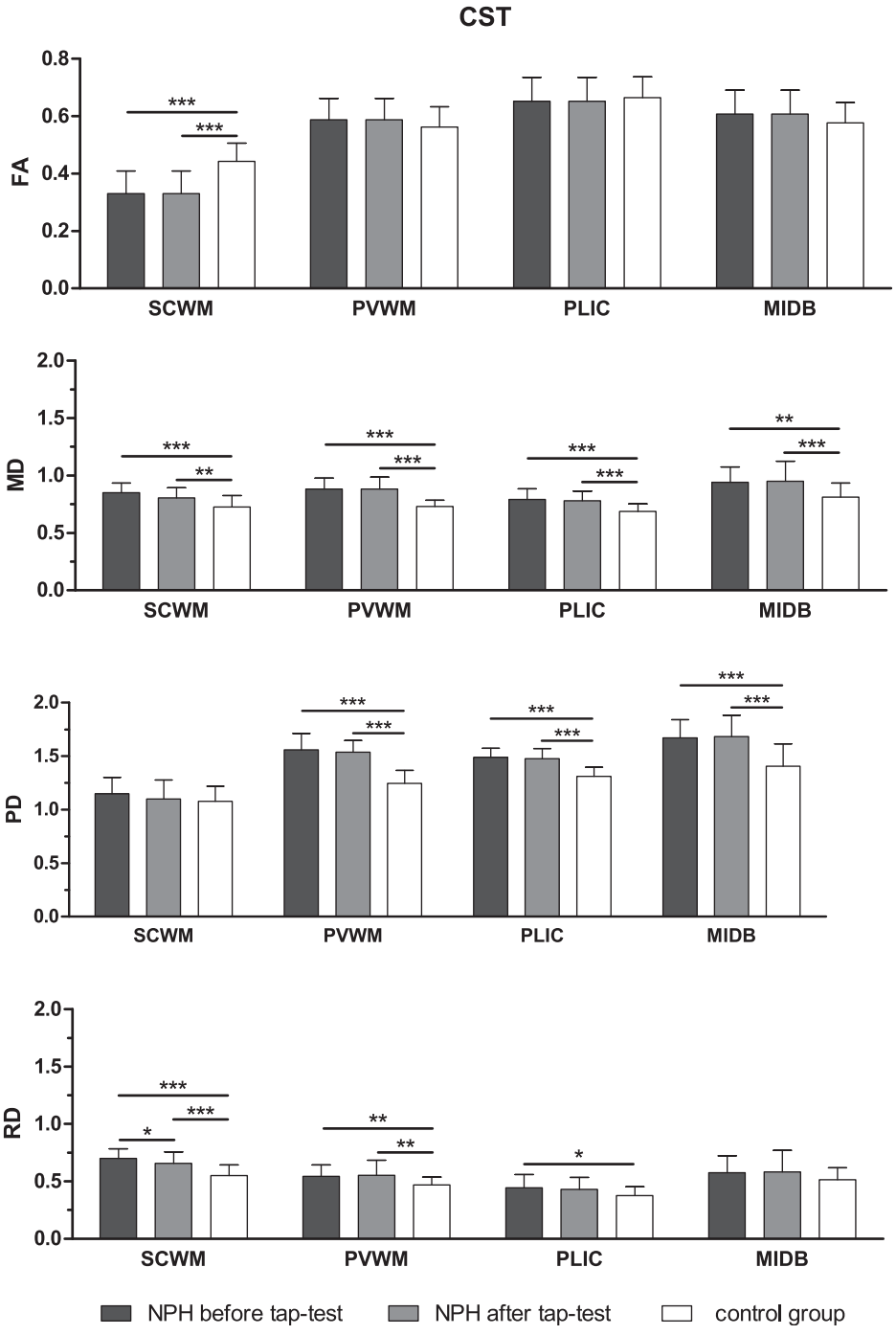

Fig. 2. DTI parameter changes in four ROI along the corticospinal tract. MD, PD, and RD values in 10^{-3} mm^2/s (mean ± SD). Stars indicate different significance levels (*<0.05, **<0.01, ***<0.001).

patients with suspected iNPH before and after CSF withdrawal test, which is mainly driven by a significant increase of the RD outbalancing the rather slight increase of the PD. These findings were consistent for both ROI and TBSS analysis and are in concordance with recently reported findings (19). In the ROI analysis we also found a marginal significant increase ($P = 0.046$) of the RD before tap-test compared to the examination after CSF withdrawal test. Although these findings were not confirmed in the TBSS analysis, this might indicate enhanced functional connectivity of the lower-body corticospinal tract after decompression of periventricular fiber tracts by CSF drainage, accounting for improved gait (23). Lenfeldt et al. proposed that the elevated MD in the pre-central white matter is indicative for an abnormal water concentration not

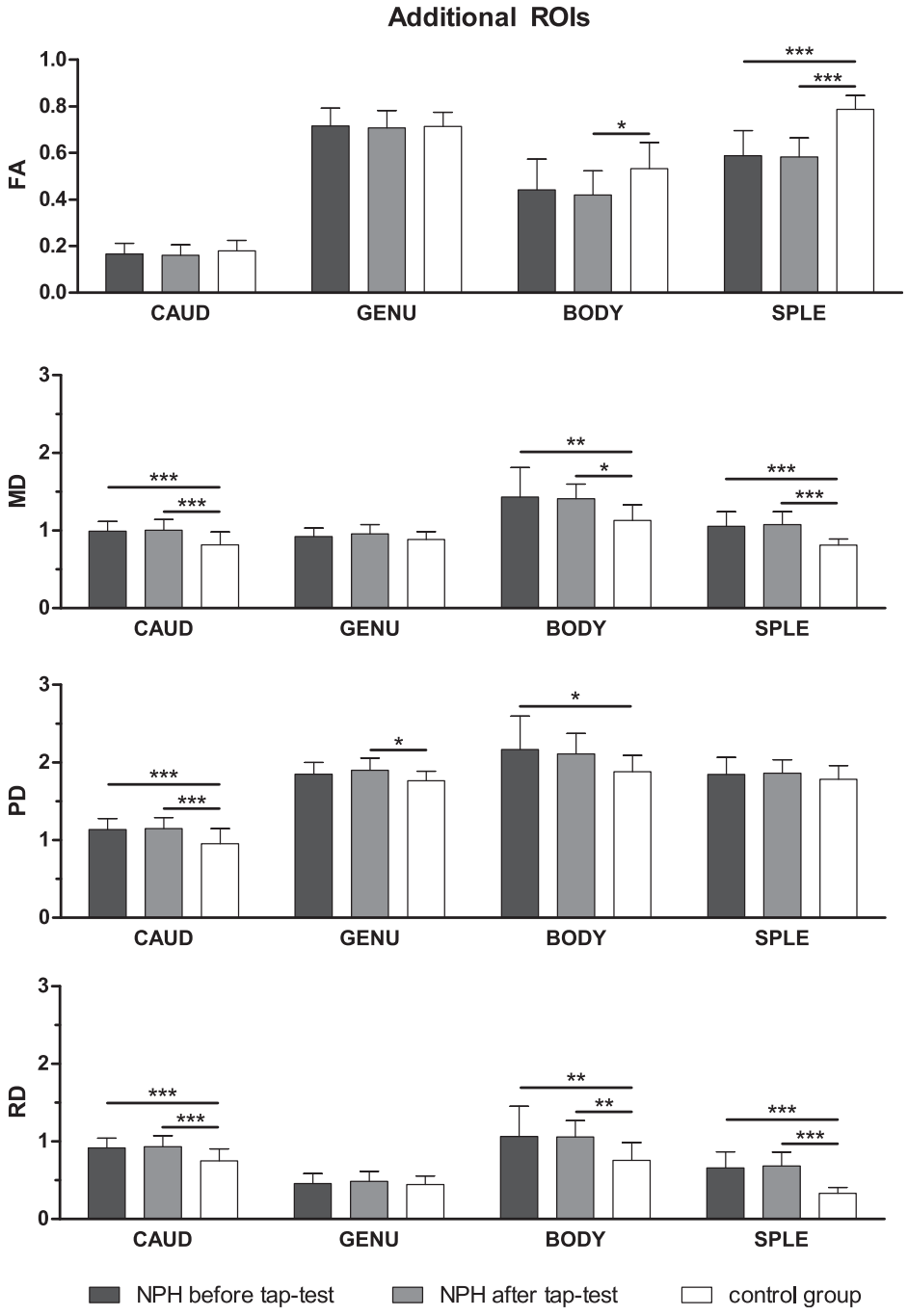

Fig. 3. DTI parameter changes in the corpus callosum and the head of the caudate nucleus. MD, PD, and RD values in $10^{-3}\,mm^2/s$ (mean $\pm$ SD). Stars indicate different significance levels (*$<$0.05, **$<$0.01, ***$<$0.001).

resulting in discernible white matter lesions, and that axonal integrity remains preserved (19). Using transcranial magnetic stimulation in hydrocephalic patients, Röricht et al. demonstrated that normal corticospinal and callosal conduction times exclude degeneration, demyelination, or functional block of a large proportion of callosal or corticospinal fibers (24). These findings strengthen the assumption that a reduction of FA and increase of MD in patients with iNPH is an effect of increased interstitial fluid with potential normalization after implantation of a ventriculo-peritoneal shunt. They further assumed that motor disturbances in patients with hydrocephalus are due to an impairment of ipsilateral or trans-callosally crossing connections between the basal ganglia and the primary or premotor cortex. The assumed dysfunction of cortico-basal ganglia-thalamo-cortical circuits with special involvement of frontal areas is considered as the

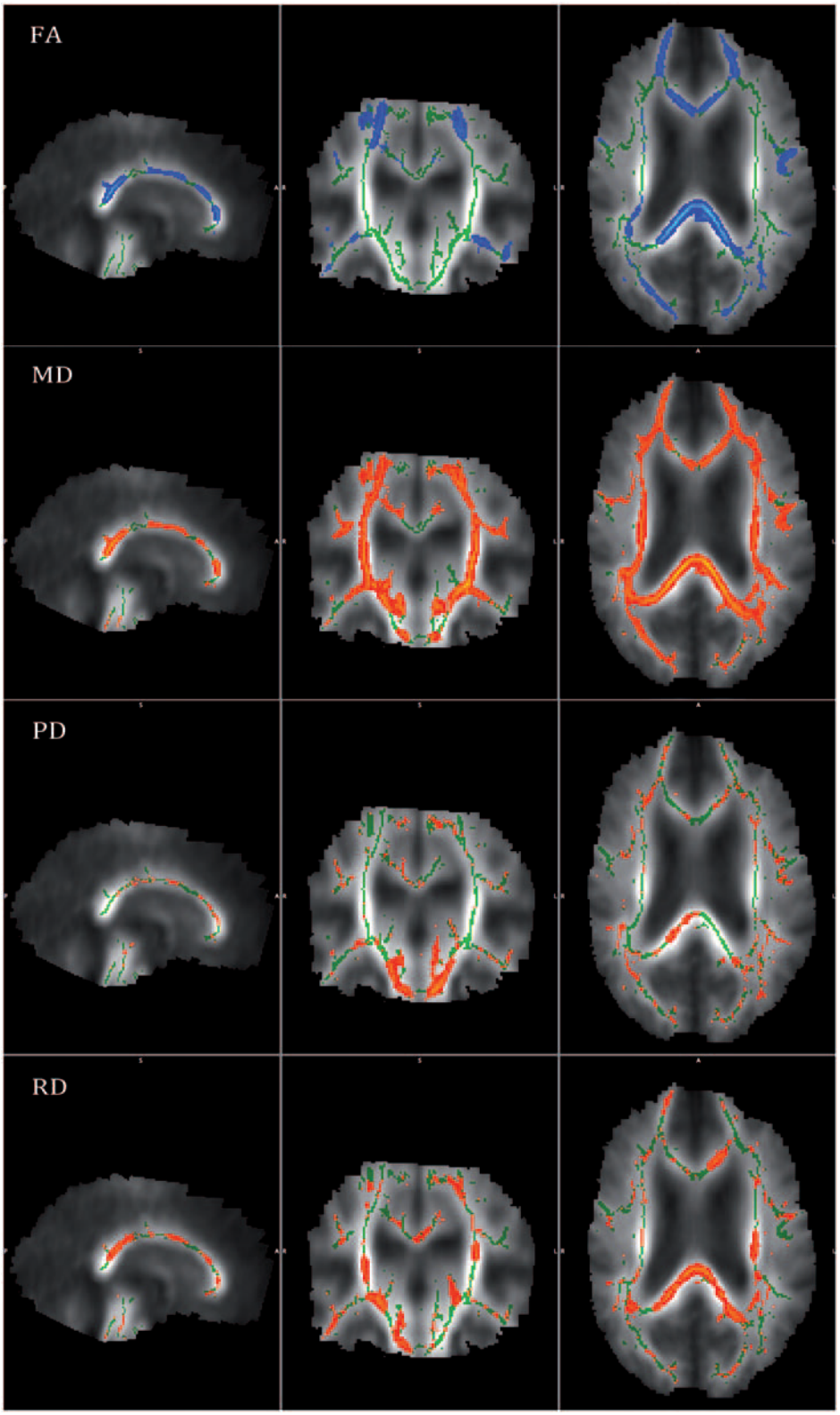

Fig. 4. Results of the TBSS analysis of patients before CSF withdrawal test and healthy control group for FA, MD, PD, and RD values. Please note the general increase (red) of the MD values throughout the periventricular white matter and to a lesser extent in the PD and RD values. The FA values are decreased (blue), especially in the corpus callosum and the subcortical white matter.

reason for the view of iNPH as a hypokinetic condition in recent literature (25,26). Current findings of enhanced activity of the supplementary motor area in fMRI studies after CSF removal as well as improvement of regional cerebral blood flow in mesial frontal areas support this hypothesis (27,28). The reduction towards normalization of RD in the subcortical white matter observed in our patients after CSF withdrawal is considered to support the above-cited findings.

Further down the CST, previous studies found a broad variation in FA, mainly being normal or increased, which has been suggested to be related to compression of the passing fibers, increasing their parallelism and density (5,11,20). These results are in accordance with our observations.

Ventricular enlargement leads to stretching and compression of the corpus callosum in iNPH (24,29), which may result in axonal loss and Wallerian degeneration of the interhemispheric fibers (30). The distension and thinning of the CC in conjunction with axonal degeneration may result in a reduced packing of the fibers, which leads to a decrease of the FA (5,11,31).

There are only two recently published studies comparing patients with suspected and confirmed iNPH before and after CSF withdrawal test (19,32). Lenfeldt et al. found no significant changes in FA and MD using a ROI-based analysis of the CST and periventricular regions. Demura et al. subdivided the cohort into a positive group characterized by neurological improvement after CSF withdrawal test and a negative one without improvement. After CSF withdrawal test, MD values were significantly decreased in the frontal periventricular region and the body of the CC in the positive group, whereas no significant changes were shown in the negative group. Although we did not subdivide our patients into groups due to the limited number of patients, we also found a trend towards a decrease of the MD in the subcortical white matter after withdrawal test, mainly driven by a decrease of the RD. The decrease of MD might be due to normalization of the volumes of the lateral ventricles and a subsequent increase of the brain volume adjacent of the ventricles as well as in temporal and frontal areas after CSF withdrawal (33). This suggests that changes of water dynamics in white matter may have a role in the mechanism leading to symptomatic iNPH.

As in most iNPH studies, the interpretation of these results is limited by the selection of patients, since there are no definite inclusion or exclusion criteria for iNPH. Due to the moderate sample size we did not analyze groups with neurological improvement after CSF withdrawal test or implantation of a ventriculo-peritoneal shunt system. A potentially confounding factor may arise from the selection of control subjects. In our study, the focus was set on analyzing possible differences of diffusion before and after CSF withdrawal test. The control group mainly served as a tool of validation for imaging and postprocessing techniques.

In conclusion, DTI in patients with suspected iNPH reveals significant changes of diffusion parameters compared to a control group. FA, MD, PD and RD may change in different directions and to a different extent depending of the specific location. The underlying, obviously multifactorial mechanisms of these alterations are still not fully understood. It seems that even a one-stage decompression by CSF withdrawal test leads to a decrease of interstitial water deposition in the frontal white matter including periventricular and extrapyramidal components, which may explain the improvement of gait.

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