

ORIGINAL RESEARCH

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Is cerebral edema effective in idiopathic intracranial hypertension pathogenesis?: Diffusion weighted MR imaging study

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Abstract

The aim of this study is to research whether cerebral edema is effective in the pathogenesis of patients with idiopathic intracranial hypertension (IIH) by using diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements. Thirty-six IIH patients who received DWI and 36 age- and sex-matched healthy control group were assessed retrospectively. ADCmin, ADCmean, and ADCmax values were measured from different regions of the brain for both IIH patients and the control group. The Student's t-test was used to compare the ADCmin, ADCmax, ADCmean values acquired from distinct parts of the brain parenchyma of IIH patients with the values of control group. No significant difference was found between ADCmin, ADCmax, and ADCmean values of IIH and control group in bilateral frontal, parietal temporal and occipital lobe cortical and subcortical white matter, caudate nucleus head, putamen, thalamus, corpus callosum splenium and genu ($P>0.05$). This study showed that cerebral edema cannot be a significant mechanism in the pathogenesis of IIH.

Keywords: Diffusion-weighted imaging, apparent diffusion coefficient, idiopathic intracranial hypertension, cerebral edema

Introduction

Idiopathic intracranial hypertension (IIH) is a neurological disease characterized by increased intracranial pressure (ICP) in which cerebrospinal fluid (CSF) component is normal and the etiology of which is not known [1-3]. The most common symptom in IIH is headache, permanent or temporary sight disturbance, back and neck pain, and pulsatile tinnitus. Comorbid findings are papilledema and increased CSF pressure [4-6]. Although the definitive pathophysiology of IIH is still unknown, cerebral edema, increased cerebral blood flow, increase in CSF production, CSF outflow obstruction and increase in venous sinus pressure are among potential pathogenic mechanisms [6,7].

Although Sahs et al. [8] found histological proof about cerebral edema in post-mortem in patients with IIH, Wall et al. [9] could not find histological proof of cerebral edema. In patients with IIH, the presence of cerebral edema and its role in increased intracranial

pressure can be evaluated non-invasively with diffusion weighted imaging (DWI) techniques which characterize the diffusion features of water molecules in the brain. Apparent diffusion coefficient (ADC), which is obtained from DWI, measures the isotropic total size of water diffusion in tissue and gives quantitative information about free water fraction which includes extracellular and intracellular water in the tissue [10]. A few previous DWI studies showed that IIH patients have a convective transependymal water flow which causes cerebral edema [11-13]. However, some diffusion studies reported that cerebral edema is not a factor in IIH pathogenesis [14-16]. It is not yet clear whether cerebral edema is effective in IIH pathogenesis due to the inconsistency of studies conducted on the subject so far. Recent studies conducted with DWI reported that minimum ADC (ADCmin) values are superior to mean ADC (ADCmean) and maximum ADC (ADCmax) values in differentiating high-grade glioma from solitary metastases [17,18] and low-grade meningioma from high-grade meningioma [19,20]. To the best of our knowledge, there are no studies in literature which have reported the use of MR diffusion metrics including ADCmin, ADCmax, and ADCmean parameters to research whether cerebral edema is effective in the pathogenesis of IIH.

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The aim of this study is to research whether cerebral edema has a role in the pathogenesis of IIH patients by using DWI and ADCmin, ADCmean, and ADCmax measurements.

Material and Methods

Patients

This study was approved by the local ethics committee of our institution. Electronic medical records (March 2015 - February 2018) were used for this retrospective study. Patients were first identified in the electronic medical records database by searching for the keywords “idiopathic intracranial hypertension”. Seventy-four patients were determined retrospectively. Only the patients who had a definitive diagnosis of IIH fulfilling the revised Dandy criteria [21] and those with minimum age of 18 were included in the study (n=55). Of these, 13 patients were excluded due to the following exclusion criteria: cerebral vascular disease (n=2), pregnancy (n=1), history of head trauma (n=1), neurological or psychiatric disease (n=2), other severe medical disease (n=3), alcohol or drug dependency (n=1), incidentally found arachnoid cyst (n=1) and cerebral atrophy (n=2). In addition, 4 patients were excluded since they did not have DWI and 2 patients were excluded since their DWI had obvious artefacts. Finally, 36 patients (5 men, 31 women; mean age [$\pm$ SD], 35.1 ± 5.3 years) were included in the study. All of these patients had one or more MR findings [optic nerve sheath distension (21/36), intraocular protrusion of prelaminar optic nerve (7/36), tortuosity of optic nerve (12/36), and partially empty sella (15/36)] supporting IIH diagnosis (Figure 1). In all IIH patients, CSF opening pressures were measured by LP. The mean CSF opening pressure was 34.9 ± 5.7 cm H₂O.

The control group consisted of 36 age- and sex-matched patients without brain metastases who were being investigated for staging of primary malignancies of other systems in a similar database (May 2015–June 2017) (5 men, 31 women; mean age [$\pm$ SD], 38.4 ± 6.1 years). There were no significant differences in age or sex distribution between patients with IIH and controls ($p=0.34$; $p=1.000$, respectively). These patients not suffered from neurological disorders. Brain MRIs of these patients were reported to be normal in neuroradiology department. In addition, electronic medical records of all control patients were reviewed and the patients who had the specified IIH diagnosis were excluded from the control group.

MR Imaging

DWI was performed with a single-shot spin-echo EPI (repetition time/ echo time: 3376/74 ms, section thickness: 5 mm, field of view: 230, matrix: 128x128, number of excitations: 2, intersection gap: 1 mm, b values: 0 and 1000 s/mm², scanning time: 1 min 02 s). ADC maps were automatically generated.

Image Analysis

DWI datasets were transferred to the workstation. Aneuroradiologist who was unaware to the clinical symptoms of the IIH patients and control groups reviewed the DWI independently and randomly. Since cortex and white matter distinction was not made clearly over ADC maps for both IIH patients and the control group, T2 weighted sequence was used as reference imaging. Quantitative ADCmin, ADCmean, and ADCmax values were measured with regions of interest (ROIs) from brain regions (bilateral frontal, parietal, temporal, and occipital lobe cortical and subcortical white

matter, caudate nucleus head, putamen, thalamus, corpus callosum splenium and genu) similar to Giedon et al. [13] and Bastin et al.'s [14] studied (Figure 2). ROI area was between 17 and 86 mm² (mean 37 ± 4 mm²).

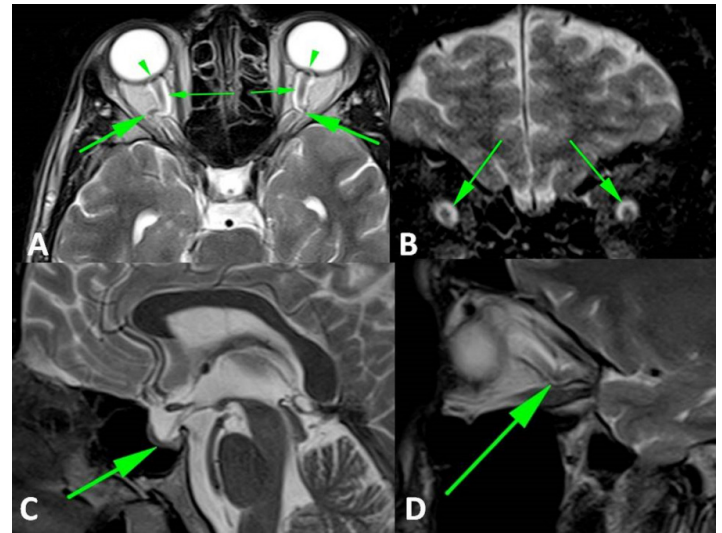


Figure 1. Qualitative MRI signs in a 35-year-old female patient with idiopathic intracranial hypertension. A, Axial T2-weighted image shows bilateral distension of the perioptic subarachnoid space (thin green arrows), bilateral intraocular protrusion of prelaminar optic nerve (arrowheads), and bilateral tortuosity of optic nerve (thin green arrows). B, Coronal fat-suppressed T2-weighted image shows bilateral distension of the perioptic subarachnoid space (thin green arrows). C, Sagittal T2-weighted image shows partially empty sella (thin green arrow). D, Sagittal T2-weighted image shows bilateral tortuosity of optic nerve (green arrow).

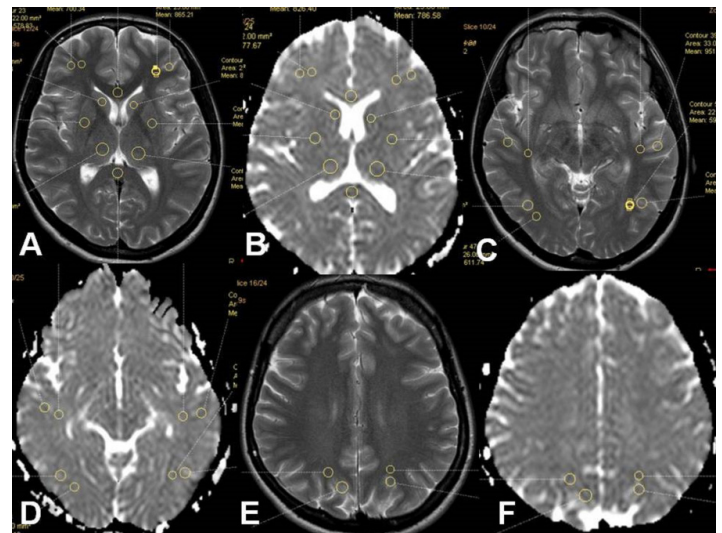


Figure 2. ROI measurement areas of a 21-year-old female IIH patient hand-drawn circular regions of interest (ROIs) through T2 weighted sequence were placed automatically on same localization and same size ADC maps. In T2-weighted (A) and ADC maps (B), there are hand-drawn circular ROIs in bilateral putamen, caudate nucleus head, thalamus, corpus callosum splenium and genu, frontal cortical and subcortical white matter. In T2-weighted (C) and ADC maps (D), there are ROIs in bilateral temporal and occipital cortical and subcortical white matter. In T2-weighted (E) and ADC maps (F), there are ROIs in bilateral parietal cortical and subcortical white matter.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics version 21; IBM, Armonk, NY, USA). The Student's t-test was used to compare

the ADCmin, ADCmax, ADCmean values acquired from distinct parts of the brain parenchyma of IHH patients with the values of control group. P values less than 0.05 were considered statistically significant.

Results

Table 1 shows the demographic and clinical characteristics of IHH patients and the control group. There were no significant differences in age or sex distribution between patients with IHH and controls ($p=0.34$; $p=1.000$, respectively). The mean CSF opening pressure was 34.9 ± 5.7 cm H₂O.

Parenchymal abnormality was not found in conventional MRI and DWI sequences off all IHH patients and the control group.

Table 2 summarizes the quantitative values containing mean and

related statistical analysis of ADCmin, ADCmax and ADC mean values, in different brain regions for IHH and control group. There was no statistically significant difference between ADCmin, ADCmax, and ADCmean values of IHH and control group in bilateral frontal, parietal, temporal, and occipital lobe cortical and subcortical white matter, caudate nucleus head, putamen, thalamus, corpus callosum splenium and genu ($P>0.05$).

Table 1. Demographic and clinical characteristics of the participants

	IHH (Mean $\pm$ SD)	Control group (Mean $\pm$ SD)	p value
Age (years)	35.1 $\pm$ 5.3	38.4 $\pm$ 6.1	0.342
Gender, Females/Males	31/5 (86%/14%)	31/5 (86%/14%)	1.00
CSF pressure (cmH ₂ O)	34.9 $\pm$ 5.7	NA	
Idiopathic intracranial hypertension (IHH). NA not applicable			

Table 2. Mean ADCmin, ADCmax, and ADCmean values for IHH patients and control group*

Region	ADCmin			ADCmax			ADCmean		
	IHH	Control	p	IHH	Control	p	IHH	Control	p
Frontal CX R	0.622	0.643	0.52	0.951	0.927	0.56	0.788	0.772	0.58
Frontal CX L	0.634	0.609	0.44	0.932	0.914	0.48	0.803	0.781	0.42
Frontal SWM R	0.575	0.590	0.26	0.860	0.897	0.16	0.709	0.724	0.52
Frontal SWM L	0.562	0.587	0.11	0.901	0.883	0.34	0.695	0.718	0.40
Parietal CX R	0.604	0.623	0.47	0.997	0.952	0.07	0.801	0.789	0.55
Parietal CX L	0.629	0.656	0.08	0.976	0.944	0.28	0.808	0.795	0.58
Parietal SWM R	0.554	0.579	0.10	0.823	0.848	0.22	0.686	0.709	0.26
Parietal SWM L	0.542	0.568	0.07	0.849	0.832	0.44	0.672	0.694	0.22
Temporal CX R	0.638	0.663	0.14	1.021	0.967	0.10	0.816	0.761	0.07
Temporal CX L	0.621	0.659	0.08	0.943	0.965	0.31	0.787	0.803	0.38
Temporal SWM R	0.539	0.557	0.31	0.833	0.851	0.41	0.721	0.699	0.34
Temporal SWM L	0.567	0.596	0.07	0.873	0.859	0.55	0.716	0.702	0.41
Occipital CX R	0.617	0.641	0.10	0.933	0.951	0.42	0.782	0.811	0.12
Occipital CX L	0.597	0.628	0.09	0.955	0.932	0.36	0.791	0.801	0.44
Occipital SWM R	0.514	0.529	0.20	0.825	0.842	0.44	0.702	0.684	0.42
Occipital SWM L	0.525	0.546	0.26	0.858	0.827	0.16	0.679	0.711	0.11
CC splenium	0.503	0.531	0.20	0.802	0.841	0.26	0.682	0.696	0.38
CC genu	0.478	0.497	0.11	0.785	0.809	0.35	0.639	0.620	0.31
Thalamus R	0.578	0.545	0.18	0.912	0.878	0.31	0.742	0.751	0.44
Thalamus L	0.592	0.561	0.22	0.911	0.873	0.20	0.758	0.776	0.24
Head of caudate R	0.580	0.552	0.07	0.876	0.900	0.31	0.743	0.770	0.07
Head of caudate L	0.557	0.541	0.35	0.860	0.895	0.20	0.750	0.779	0.10
Putamen R	0.565	0.587	0.22	0.843	0.875	0.26	0.705	0.722	0.45
Putamen L	0.582	0.556	0.20	0.824	0.850	0.31	0.715	0.741	0.31

*Except for the p-values, minimum, maximum, and mean apparent diffusion coefficient (ADCmin, ADCmax, and ADCmean) (s/mm²), idiopathic intracranial hypertension (IHH), right cortex (CX R), left cortex (CX L), right subcortical white matter (SWM R), left subcortical white matter (SWM L), corpus callosum (CC).

Discussion

IIH is a cerebral intracranial pressure increase with normal CSF compound which is not dependent on a secondary reason (the reason of which is not found). In IIH, neuroimaging findings are optic nerve sheath distension, intraocular protrusion of prelaminar optic nerve, tortuosity of optic nerve, and partially empty sella [22,23]. Despite the increasing number of researches, the pathophysiology underlying IIH has not been completely clarified. Among these, cerebral edema is remarkable.

In the current study, I researched whether cerebral edema can play a role in the pathogenesis of patients with IIH with quantitative ADC measurements by using DWI. No statistically significant difference was found in ADCmin, ADCmax, and ADCmean values of different regions of the brain between healthy control group and IIH ($P > 0.05$). These results can bring to mind that cerebral edema does not play a role in IIH pathogenesis.

DWI measures the random translational motion of water molecules in biological tissues of ADC isotropic quantitatively and reflects some pathological states in the brain [24, 25]. This way, ADC gives clues about the cellularity of the tissue, interstitial distance, myelination degree and the microstructural organization of white matter tracts. Increase in water diffusion in interstitial distance in white matter tracts results in ADC increase [26]. Water diffusion is anisotropic in cerebral white matter. For this reason, water diffusion is restricted perpendicularly, while it is not restricted in parallel direction in white matter tracts. Water diffusion in gray matter is not restricted [27]. Some of the DWI studies in IIH patients reported ADC increase in some regions of the brain, which indicates cerebral edema [11-13]. In their two studies, Sorensen et al. [11,12] compared IIH patients with the control group and reported periventricular increased water diffusion in some patients while they reported increased water diffusion in the whole brain in other patients. Thus, they reported that IIH patients have a convective transependymal water flow and intracellular brain water accumulation which causes cerebral edema. Partly supporting this hypothesis, Gideon et al. [13] showed increase in ACD values associated with increased water diffusion in subcortical white matter in IIH patients when they were compared with the control group. However, they did not find significant ADC increase in other regions of the brain in IIH patients. As a result, unlike my study, these studies reported significant increase in some regions of the brain in IIH patients when compared with the control group.

Some of the DWI studies which examined whether cerebral edema was a factor in the pathogenesis of IIH patients could not find diffusion abnormalities signaling brain edema in the patients [14-16]. Bastin et al. [14] demonstrated that no significant difference between IIH patients and the control group in the average diffusivity of water in any region of the brain and they reported that diffuse brain edema was not a feature of IIH. Similarly, Bicakci et al. [16] did not find any diffusion anomaly in IIH patients with DWI. However, they did not conduct quantitative assessment in their study. Similarly, in the current study no significant difference was found between ADC values of IHH patients and control group in different regions of the brain including bilateral frontal, parietal temporal and occipital lobe cortical and subcortical white matter, caudate nucleus head, putamen, thalamus, corpus callosum splenium and genu ($P > 0.05$). Owler et al. [15] showed that when

compared with the control group, diffusion parameters in putamen and head of the caudate nucleus increased in IIH patients; however, no significant differences were found in thalamus, cerebral white matter or cortical regions. They reported that cerebral edema was not a factor in the pathogenesis of IIH. Schmidt et al. [28] did not find significant differences in fractional anisotropy (FA) and mean diffusivity (MD) values between IIH patients and the control group by using diffusion tensor imaging. Although FA and MD have very high sensitivity in microstructural changes, they are not very specific. Recently directional diffusivity metrics radial and axial diffusivity (RD and AD) have been used to better characterize WM microstructure and to maximize specificity [29]. Tract-based spatial statistics (TBSS) is the voxel wise statistical analytical method developed to assess DTI metrics (FA, MD, RD, AD). TBSS can assess automatic, operator-independent whole-brain WM integrity [30]. Future studies can assess with TBSS whether cerebral edema is effective in the pathogenesis of IIH patients.

To the best of our knowledge, this is the first study reporting ADCmin values in researching cerebral edema in IIH pathogenesis. In my study, no difference was found between ADCmin, ADCmax and ADCmean values in different regions of the brain in IIH patients ($P > 0.05$). Although there were no statistically significant differences in ADCmin, ADCmean and ADCmax values between IIH patients and the control group, ADCmin values were found to be superior to ADCmean and ADCmax values. In the current study, the results brought to mind that cerebral edema cannot have a role in IIH pathogenesis.

There were some limitations in the study. First of all, since it was a retrospective study, BMI index was not known for the patient and the control group. In order to confirm the results of our study, prospective studies which measure BMI index for the patient and the control group are needed. Secondly, lumbar puncture was not performed on the healthy control group. In addition, the whole healthy control group did not show any signs of intracranial pressure increase (headache, impaired sight) and since they did not have OCT screening, papilledema symptom is not probable. Lastly, some of the IIH patients did not have (n=15) MR venography. However, despite being highly unlikely, I may therefore have missed small venous pathologies.

Conclusion

In this study, no significant difference was found between the ADCmin, ADCmax and ADCmean values obtained from the certain diverse regions of the brains of IHH patients compared to the normal healthy control group. The results of this study suggested that cerebral edema cannot be an important mechanism in IIH pathogenesis. In the next step, whole brain DTI studies are required which are conducted with diffusion parameters including axial and radial diffusivity which are more specific when compared with microstructural tissue changes.

Financial Disclosure

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Ethical approval

This work has been approved by the Institutional Review Board.

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References

1. Wall M. Update on Idiopathic Intracranial hypertension. *Neurol Clin.* 2017;35:45-57.
2. Dhungana S, Sharrack B, Woodroffe N. Idiopathic intracranial hypertension. *Acta Neurol Scand.* 2010;121:71–82.
3. McCluskey G, Mulholland DA, McCarron P, et al. Idiopathic Intracranial Hypertension in the Northwest of Northern Ireland: Epidemiology and Clinical Management. *Neuroepidemiology.* 2015;45:34-9.
4. Ball AK, Clarke CE. Idiopathic intracranial hypertension. *Lancet Neurol.* 2006;5:433-42.
5. Wall M, George D. Idiopathic intracranial hypertension: a prospective study of 50 patients. *Brain.* 1991;114:155-80.
6. Markey KA, Mollan SP, Jensen RH, et al. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. *Lancet Neurol.* 2016;15:78-91.
7. Skau M, Brennum J, Gjerris F, et al. What is new about idiopathic intracranial hypertension? An updated review of mechanism and treatment. *Cephalalgia.* 2006;26:384-99.
8. Joynt RJ, Sahs AL. Brain swelling of unknown cause. *Neurology.* 1956;6:801-3.
9. Wall M, Dollar JD, Sadun AA, et al. Idiopathic intracranial hypertension. Lack of histologic evidence for cerebral edema. *Arch Neurol.* 1995;52:141-5.
10. Le Bihan D, Breton E, Lallemand D, et al. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology.* 1988;168:497–505
11. Sorensen PS, Thomsen C, Gjerris F, et al. Increased brain water content in pseudotumour cerebri measured by magnetic resonance imaging of brain water self-diffusion. *Neurol Res.* 1989;11:160–4.
12. Sorensen PS, Thomsen C, Gjerris F, et al. Brain water accumulation in pseudotumour cerebri demonstrated by MR-imaging of brain water self-diffusion. *Acta Neurochir Suppl (Wien).* 1990;51:363–5.
13. Gideon P, Sorensen PS, Thomsen C, et al. Increased brain water self-diffusion in patients with idiopathic intracranial hypertension. *Am J Neuroradiol.* 1995;16:381–7.
14. Bastin ME, Sinha S, Farrall AJ, et al. Diffuse brain edema in idiopathic intracranial hypertension: a quantitative magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry.* 2003;74:1693-6.
- 15.owler BK, Higgins JN, Péna A, et al. Diffusion tensor imaging of benign intracranial hypertension: absence of cerebral oedema. *Br J Neurosurg.* 2006;20:79-81.
16. Bicakci K, Bicakci S, Aksungur E. Perfusion and diffusion magnetic resonance imaging in idiopathic intracranial hypertension. *Acta Neurol Scand.* 2006;114:193-7.
17. Han C, Huang S, Guo J, et al. Use of a high b-value for diffusion weighted imaging of peritumoral regions to differentiate high-grade gliomas and solitary metastases. *J Magn Reson Imaging.* 2015;42:80-6.
18. Lee EJ, terBrugge K, Mikulis D, et al. Diagnostic value of peritumoral minimum apparent diffusion coefficient for differentiation of glioblastoma multiforme from solitary metastatic lesions. *AJR Am J Roentgenol* 2011;196:71–6.
19. Watanabe Y, Yamasaki F, Kajiura Y, et al. Preoperative histological grading of meningioma's using apparent diffusion coefficient at 3T MRI. *Eur J Radiol.* 2013;82:658-63.
20. Aslan K, Gunbey HP, Tomak L, et al. The diagnostic value of using combined MR diffusion tensor imaging parameters to differentiate between low- and high-grade meningioma. *Br J Radiol.* Published Online: 31.05.2018
21. Wall M, Corbett JJ. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2014;83;198-9.
22. Raoof N, Sharrack B, Pepper IM, et al. The incidence and prevalence of idiopathic intracranial hypertension in Sheffield, UK. *Eur J Neurol.* 2011;18:1266–8.
23. Friedmann DI, Liu GT, Digre KB. Revised criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology.* 2013;81:1159–65.
24. Kanaan RA, Shergill SS, Barker GJ, et al. Tract-specific anisotropy measurements in diffusion tensor imaging. *Psychiatr Res.* 2006;146:73–82.
25. Mukherjee P. Diffusion tensor imaging and fiber tractography in acute stroke. *Neuroimaging Clin North Am.* 2005;15:655–65.
26. Salvay DM, Padhye LV, Huecker JB, et al. Correlation Between Papilledema Grade and Diffusion-Weighted Magnetic Resonance Imaging in Idiopathic Intracranial Hypertension. *J Neuroophthalmol.* 2014;34:331-5.
27. Hajnal JV, Doran M, Hall AS, et al. MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic and pathologic considerations. *J Comput Assist Tomogr.* 1991;15:1–18.
28. Schmidt C, Wiener E, Lüdemann L, et al. Does IHH Alter Brain Microstructures? - A DTI-Based Approach. *Headache.* 2017;57:746-55.
29. Alexander AL1, Lee JE, Lazar M, et al. Diffusion tensor imaging of the brain. *Neurotherapeutics.* 2007;4:316-29.
30. Smith SM, JenkinsonM, Johansen-Berg H, et al. Tract based spatial statistics: voxel wise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–505.