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Microstructural changes of the optic nerve in idiopathic intracranial hypertension: A DTI analysis

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Abstract

Aim: We aim to investigate whether increased perioptic cerebrospinal fluid (CSF) pressure causes changes in the optic sheath diameter and microstructure of the optic nerve in patients with idiopathic intracranial hypertension (IIH). We also aim to investigate the relationship between optic sheath diameter and the optic nerve microstructural changes.

Materials and Methods: Our retrospective study is a neuroimaging study of CSF opening pressure-confirmed IIH cases and controls, including 1.5 T magnetic resonance imaging (MRI) and diffusion tensor brain imaging. The optic nerve was evaluated by region of interest (ROI) with diffusion tensor imagine (DTI) and compared with the healthy control. DTI findings were correlated with optic sheath diameters.

Results: The ADC and RD values obtained from the left optic nerve were significantly increased compared to the healthy group (p=0.004 and p=0.002, respectively). The FA values obtained from the right and left optic nerves were decreased considerably compared to the healthy group (p=0.035 and p=0.015, respectively). We found that perioptic CSF distance increased in cases with IIH and there was a negative correlation between CSF distance and both optic nerve AD values (Left r=-0.42 and right r=-0.43).

Conclusion: Patients with IIH have significant DTI changes in the optic nerve microstructure, which is related to the optical sheath diameter. It may be possible to detect optic nerve damage early with microstructural changes before permanent vision loss develops and to monitor nerve damage with DTI parameters. Early recognition of optic nerve damage due to intracranial high pressure with DTI parameters is important in preventing permanent vision loss.

Introduction

Idiopathic intracranial hypertension (IIH) is characterized by increased cerebrospinal fluid (CSF) pressure without an identifiable cause [1]. To make the diagnosis, it is necessary to exclude secondary causes by brain MRI. Increased intracranial CSF pressure is reflected in the perioptic subarachnoidal space. Edema that develops at the head of the optic nerve due to increased perioptic pressure is called papilledema. In young cases, the most common cause of papilledema is idiopathic intracranial hypertension [2]. In most cases, loss of visual function is the only significant morbidity, and bilateral blindness may develop in approximately 10% of patients [3,4].

The most common clinical findings in IIH are headache and visual disturbances due to papilledema [5]. Typical orbital MRI findings in patients with IIH include flattening at the back of the globe, protrusion of the optic nerve into the globe, and widening of the perioptic subarachnoid space [6,7]. Since CSF regions are freely interconnected, the increase in intracranial pressure is also reflected in the perioptic distance. After papilledema, axonal conduction and axoplasmic flow are impaired in the optic nerve. It is still unclear whether impaired axonal dysfunction results from physical compression of the optic nerve by increased perioptic CSF pressure or microvascular ischemia [2]. Abnormal CSF pressure pulsations have been demonstrated in patients with IIH. It is unknown whether these abnormal pressure changes cause optic nerve damage in these patients [8]. Conventional neuroophthalmic imaging findings in idiopathic intracranial hypertension have been well described in many studies, and there are very few studies in the literature on optic nerve microstructural changes [9,10,11].

DTI is an advanced neuroimaging method that examines the microstructure of axons in the white matter in a non-invasive manner and can detect white matter microstructural changes and white matter integrity before macro-

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scopic changes [12]. Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), Radial Diffusivity (RD), and Axial Diffusivity (AD) are the four most commonly used DTI parameters. FA provides information about the direction of the axon and the 3D diffusion isotropy of the water molecule. ADC is a parameter related to extracellular fluid distance. AD and RD are associated with myelination and axonal loss [13,14,15,16,17,18].

In this study, optic nerve DTI findings, and optic sheath diameters of IIH subjects confirmed by CSF opening pressure were compared with healthy controls. We aim to investigate with the DTI method whether abnormal CSF pulsations associated with increased intracranial pressure in IIH cause mechanical compression against the optic nerve, causing changes in the microstructure of the optic pathway. We also aim to investigate the relationship between optic sheath diameter and optic nerve microstructural changes. Early recognition of optic nerve damage and papilledema due to intracranial high pressure is important in preventing permanent vision loss.

Materials and Methods

Participants

All procedures performed in studies involving human participants were inaccordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Bezmialem Vakif University Ethics Committee (31.05.2024-152543). Since our study was retrospective, our ethics committee did not request written consent from the patients. For our retrospective study, patients with brain MRI were identified by searching keywords such as "Pseudotumor cerebri and intracranial hypertension" from our image archive system between 2019 and 2024, with the knowledge of our institution's ethics committee. The clinical data of these patients regarding CSF opening pressure and papilledema in our archives were scanned. Among these patients, 45 patients between the ages of 19-64 with CSF pressure data were evaluated for eligibility for the study. Twenty subjects with intracranial space-occupying lesions, previous operations, and comorbidities such as hydrocephalus, multiple sclerosis, and migraine were excluded from the study. A total of 25 (23F, 2M; mean age: 38.92 ± 8.86 years) newly diagnosed patients based on CSF pressure and brain MRI findings were included in the study. Patients without comorbidities, with high lumbar puncture opening pressure, and findings supporting intracranial hypertension on brain MRI were selected. Control group of the study was determined as follows. 28 controls (20F, 8M; mean age: 38.14 ± 10.32 years) were included among the cases with no neurological disorder, who applied to the neurology outpatient clinic due to headache, and who had no pathological findings on brain MRI.

MR imaging technique and DTI analysis

Before evaluation, all DTI images were visually scanned by an expert radiologist (SB with eight years of imaging experience). All cranial MRIs were reviewed for the presence of idiopathic intracranial hypertension. Since all cases presented with a headache or a visual impairment, images were obtained with 1.5 Tesla MRI (Avanto, Siemens Healthineers, Erlangen, Germany) during the symptomatic period. All cases were newly diagnosed. Axial T1-weighted imaging (TR/TE: 550/8 ms), axial T2-weighted imaging, and sagittal T2-weighted imaging consisting of the MRI protocol (TR/TE:4500/90). With 3 mm slice thickness, 230 mm field of view (FOV), 30 gradient directions, TR = 6,000 ms, TE = 82 ms, and b = 0 s/mm^2 and b = 1000 s/mm^2, DTI was produced using SE- EPI sequences. The matrix size was 128x128. Optic sheath diameter measurement was made on a T2-weighted sequence in the axial plane from both orbits. Optic sheath diameters were measured at its widest point, 3 mm behind the posterior wall of the globe. Optic sheath diameters were compared with healthy controls.

Our DTI examination was performed manually based on regions of interest (ROI). Using color-coded fractional anisotropy (FA), Axial Diffusivity (AD), Radial Diffusivity (RD) maps, and the apparent diffusion coefficient (ADC), DTI values were calculated using the Siemens Syngo-Via console (software version 2.0). ROIs were positioned on the Optic nerve via FA color maps. All ROIs were carefully drawn manually in an area of approximately 25 mm^2 at the designated anatomical location. Care was taken to ensure the ROIs were equally circular in size in both optic nerves. This ROI analysis is presented in Figure 1 and 2.

DTI parameters, including FA, ADC and AD values, were compared between the healthy control groups. Correlation analysis of DTI findings and optic sheath diameters were analyzed.

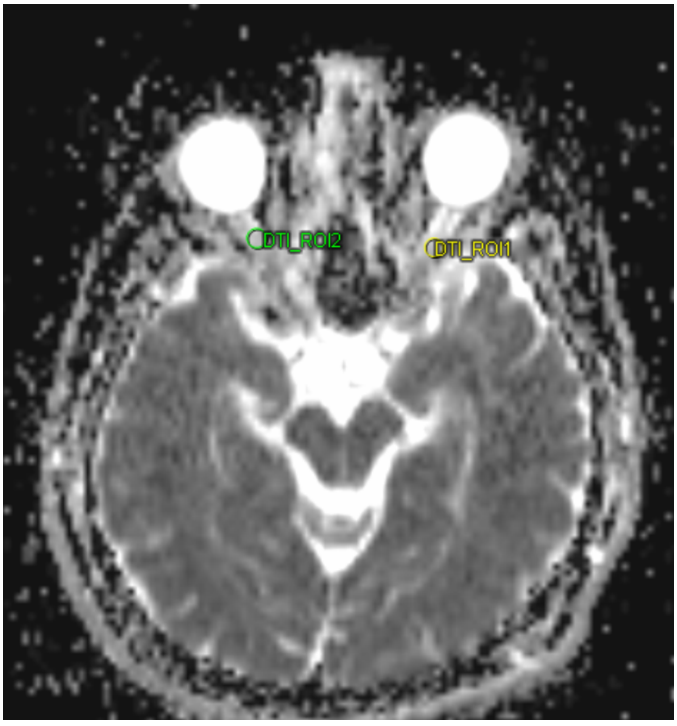

Figure 1. Placement of the ROI on the optic nerve of ADC map.

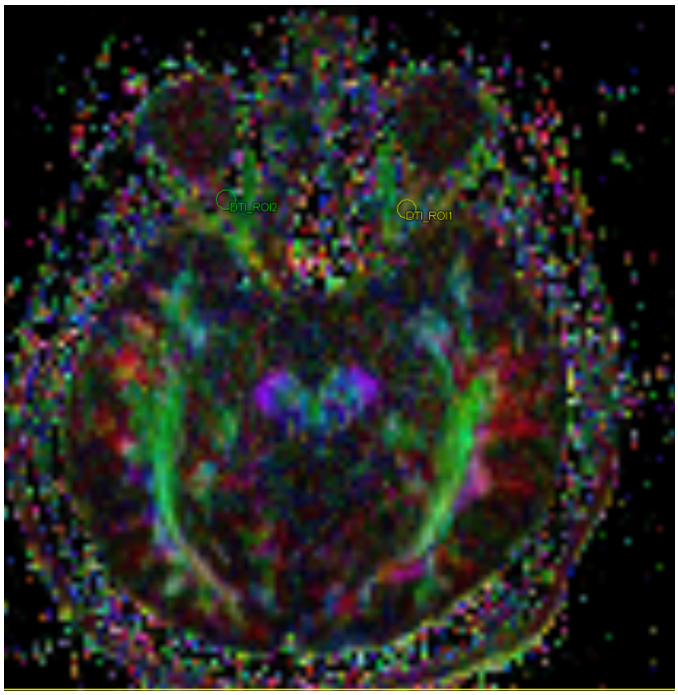

Figure 2. Placement of the ROI on the optic nerve of FA map.

Statistical analysis

Descriptive statistics were given with mean±standard deviation median(minimum-maximum) and frequencies with percentages, as n(%). Variables' distributions were examined with Shapiro-Wilks test. The variables were normally distributed, so continuous variables were compared with an Independent samples t-test, and relations were examined in idiopathic intracranial hypotension with a Pearson Correlation Coefficient. Categorcial variables group comparisons were analyzed with Fisher's Exact test. SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) software were used for analysis. Type-I error rate was taken α=0.05. Based on previous studies, with Cohen's d = 1.30 for 80% power at a 95% confidence level, a difference between means of 10.33 units, and a standard deviation of 2.12, the minimum sample size was calculated as 22. Power analysis was made with G-Power 3.1.9.7 software.

Results

Participants were 44 (83%) female, 9 (17%) male with total 53 participants and their mean age were 38.51±9.58. Right on CSF distance median was 5.90 (4.55-9.96) and left on CSF distance median was 6.34 (4.91-9.28) in participants. The ADC and RD values obtained from the left optic nerve were significantly increased compared to the healthy group (p=0.004 (-255.81-(-51.07)) and p=0.002 (-268.05-(-60.86)), respectively). The FA values obtained from the right and left optic nerve were significantly decreased compared to the healthy group (respectively; p=0.015 (10.06-87.08) and p=0.035 (3.07-83.50), respectively). The AD values obtained from the left optic nerve were significantly increased compared to the healthy group (p=0.006, (-335.58-(-59.34). The perioptic CSF distance in IIH cases was significantly increased compared to the healthy group.

Table 1. FA , ADC, RD, AD and p values obtained from right and left optic nerve in the idiopathic intracranial hypertension subjects and control group.

		Patient n:25 (Mean)	Control Group n:28 (Mean)	P-value
Right Optic Nerve	ADC	1.435	1.417	0.768
	FA	0.366	0.414	0.015
	RD	1.131	1.087	0.434
	AD	2.043	2.072	0.741
Left Optic Nerve	ADC	1.434	1.280	0.004
	FA	0.371	0.414	0.035
	RD	1.145	0.981	0.002
	AD	2.071	1.873	0.006

FA;Fractional Anisotropy ADC; Apparent Diffusion Coefficient, RD: Radial Diffusivity AD: Axial Diffusivity (x 10^{-3} mm^2/sn).

Right optic nerve sheath diameter mean values was obtained as 7.4 and 5.6 mm in IIH and control (p<0.05). Left optic nerve sheath diameter mean values was obtained as 7.5 and 5.8 mm in IIH and control (p<0.05). Detailed diffusion tensor imaging parameters for subjects and healthy controls are presented in Table 1.

Correlation analysis between perioptic CSF distance and DTI parameters

There was a negative correlation between perioptic CSF distance and right and left optic nerve AD values in cases with IIH (p=0.032, r= -0.43 and p= 0.039, r= -0.42, respectively).

Discussion

In this study, we assessed investigated the microstructure changes of the optic nerve, which is an extension of the white matter, with DTI in IIH patients. We demonstrated with MRI an increase in the diameter of the optic sheath, which we thought expanded with perioptic fluid due to increased intracranial pressure in IIH. We found lower FA values and higher ADC, RD and AD values in the optic nerve in cases with IIH compared to healthy controls. We demonstrated that as optic sheath diameter increases, optic nerve microstructural changes occur. We demonstrated that as optic sheath diameter increases, optic nerve microstructural changes. The DTI changes we found may indicate deterioration in the microstructural integrity of the optic nerve due to mechanical tissue compression due to high intracranial pressure. Decreased FA values may indicate dysmyelination and axonal loss. Increased interstitial fluid with decreased cellular density or axon number may explain the increased ADC values. Increased RD values may also indicate myelin sheath damage. These findings may indicate both axonal and myelin damage in the optic nerve in IIH patients. Schmidt et al., similar to our study, showed decreased FA values in the optic nerve in IIH patients. They suggested that these microstructural changes may underlie functional impairment of the optic nerve [11].

Studies have demonstrated that papilledema is triggered by increased intracranial pressure, which causes visual de-

terioration [5,19,20]. In orbital imaging in IIH, structural changes such as widening of the perioptic subarachnoid CSF distance, protrusion of the optic nerve into the globe, vertical tortiosity of the optic nerve, and flattening of the posterior wall of the globe are included [21,22]. Axoplasmic flow occurs due to the intraaxonal physiological pressure gradient between the ocular part and the extraocular part of the optic nerve. Increased perioptic CSF pressure increase negatively affects this physiological gradient, leading to axoplasmic stasis and papilledema. If left untreated, this CSF stasis can cause retinal congestion, ischemia, microbleeds, and ultimately optic disc atrophy and permanent blindness [23].

In another DTI study of the optic nerve in IIH, Hoffmann et al. speculated that microstructural abnormalities in the optic nerve caused by increased intracranial pressure could be reversed within hours after the pressure was reduced after a lumbar puncture. They reported decreased FA values after lumbar puncture without significant changes in ADC values. They reported that this may be due to optic nerve decompression. The same study, reported that pressure-related edema was limited to the optic nerve, especially the prelaminar optic disc and retina [10]. The fact that microstructural changes in the optic nerve in IIH are reversible after treatment, which reduces CSF pressure, increases the importance of DTI in noninvasive monitoring of treatment response in these cases. However, it is still debated whether MRI findings improve after intracranial pressure returns to normal. Therefore, studies with larger series are needed [24].

Limitations

This study has some limitations. Since our number of patients is limited, the findings need to be confirmed with a larger series of studies. Other limitations were that the DTI analysis was ROI-based and a retrospective single-center study. There may be a relationship between the duration of the disease and optic nerve damage. In addition, DTI findings may vary over time due to cases applying to our institution at different periods, which can be listed as other limitations.

Conclusion

Idiopathic intracranial hypertension is a treatable cause of headaches and can cause permanent vision loss if not diagnosed early. Therefore, it is essential to diagnose early before permanent changes develop. Although brain MRI findings in IIH have been well described in many studies, to our knowledge, there are very few DTI studies on the optic nerve in the literature. In our study, we revealed significant microstructural changes that indicate optic nerve damage due to increased intracranial pressure. DTI can help identify microstructural damage early when the optic nerve is under high pressure. It may also be helpful in quantitatively and noninvasively monitoring treatment response. In the future, large series and comprehensive cohort studies evaluating treatment response in long-term follow-up after treatment in IIH are needed.

Ethical approval

This study was approved by the Bezmialem Vakif University Ethics Committee. (31.05.2024-152543).

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