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Evaluation of cerebrospinal fluid flow parameters in primary open-angle glaucoma patients with phase contrast cine magnetic resonance imaging technique

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Abstract

This study evaluates cerebrospinal fluid (CSF) flow parameters in patients with Primary Open-Angle Glaucoma (POAG) and healthy individuals using Phase Contrast Cine Magnetic Resonance Imaging (PC Cine MRI). The study included 16 patients diagnosed with POAG and 16 healthy volunteers who had normal ophthalmologic examinations. aqueduct area, peak velocity, forward and reverse volumes, net forward volume, aqueductal stroke volume, and flow per minute were among the CSF parameters computed and compared between the POAG and healthy groups. PC Cine MRI parameters of peak velocity, average velocity, forward volume, reverse volume, net forward volume, aqueductal stroke volume, and average flow rate per minute did not differ significantly between the POAG patient and the healthy groups. However, the mean aqueduct area was significantly larger in the POAG patient group compared to the control group, and this difference remained statistically significant even after controlling for the age variable, which can affect CSF flow parameters.

Keywords: Cerebrospinal fluid pressure, phase contrast cine, glaucoma, open angle, magnetic resonance imaging

Introduction

The leading cause of blindness globally is glaucoma, which has an unclear and complex pathophysiology [1]. Although glaucoma develops due to a number of different pathophysiological processes, all types are characterized by visual field loss and characteristic changes at the optic nerve head [2,3]. The causes of primary open-angle glaucoma (POAG), a form of glaucoma frequently linked to elevated intraocular pressure (IOP), are not entirely understood [4]. It is still unclear exactly how elevated IOP damages the optic nerve [5].

The investigation of cerebrospinal fluid (CSF) flow physiology and pathologies with Phase Contrast Cine Magnetic Resonance Imaging (PC Cine MRI), sensitive even to very slow flows, has increased especially in recent years and has focused on structures such as the subarachnoid spaces, ventricular system, and spinal canal, as well as the aqueduct cerebri, where the flow exhibits the most consistent path. With the initiation of calculations of flow at the aqueduct level using numerical parameters, normal values were first understood, and then flow changes due to different pathologies were examined. Among the pathologies examined, normal pressure hydrocephalus, arachnoid cysts, and Chiari malformation are the most prominent [6-9]. Additionally, PC Cine MRI studies have been conducted regarding neuro-Behçet's disease and multiple sclerosis [10,11].

While research on the connection between POAG and CSF pressure has been published, to our knowledge, no literature has evaluated CSF flow dynamics in this patient group using PC Cine MRI, a non-invasive imaging method. This investigation's goal is to assess the dynamics of CSF flow in both healthy individuals and patients with POAG.

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Material and Methods

Patient Population

The İnönü University Clinical Research Ethics Committee gave its approval for this prospective study (Decision date: 10 January 2018; Decision number: 2018/05). The participants gave written informed consent before the study began. The research was carried out in accordance with the Declaration of Helsinki. The study included sixteen patients with POAG who visited the Ophthalmology Department of the University Faculty of Medicine and sixteen healthy individuals who underwent routine eye exams. All cases underwent corrected and uncorrected visual acuity, IOP using applanation tonometry, central corneal thickness using the Pentacam-Scheimpflug method, anterior segment examinations, and angle examinations with biomicroscopy, followed by detailed fundus and optic disc examinations with pupillary dilation, and the retinal nerve fiber layer thickness analysis with an optic coherence tomography device.

PC Cine MRI Technique

The study's participants were split into two groups (the POAG patient group and the control group). MR images were obtained using PC Cine MR angiography with a standard head coil on a 3.0-Tesla (T) system (Magnetom® Skyra, Siemens Healthcare, Germany) in axial planes. FLAIR MRI, PC Cine MRI, and T2 3D constructive interference in steady state scans were performed on the patients. The PC Cine MRI scan took approximately 6 minutes for each patient. The PC Cine MRI sequences had the following scan parameters: repetition time, 21.10 ms; echo time, 6.38ms; section thickness, 6 mm; number of signal averages, 1; field of view, 160 mm; matrix size, 205 x 256; flip angle, 10°. In a cardiac cycle, 40 sections were obtained. Cardiac triggering was performed retrospectively using finger plethysmography. To avoid outcomes that might vary with circadian rhythm, all scanning was performed between 08:00 and 16:00.

MRI Analysis

The post-processing software 'Syngo.via Siemens Healthcare' was used to transfer the MRI to a special workstation. The processing of images obtained from flash through-plane and inplane sequences took place at the MR Cardiac Analysis program to obtain phase, rephase, and magnitude images in the semi-axial and sagittal planes. In all cases, CSF flow was first visually evaluated using cine images. In rephase and magnitude images, flow within the cerebral aqueduct was observed at a high signal intensity throughout all sections. In phase images, flow in the craniocaudal direction exhibited high signal intensity, whereas flow in the caudocranial direction showed low signal intensity [12,13]. In flash (Venc 20 cm/s) through-plane semi-axial phase images, the aqueduct was magnified to optimally visualize it, and a Region of Interest (ROI) was placed that did not exceed the aqueduct boundaries and encompassed the entire aqueduct. The placed ROI was copied to the existing 40 sections. Then, to eliminate artifacts that might originate from static surrounding soft tissues, an additional ROI was drawn around the selected ROI using 'background phase adjustment', and the subtraction process was performed by the program. In this way, changes in CSF flow parameters over time during a cardiac cycle were obtained from data tables and graphs containing the following: Peak Velocity (cm/sec), Average Velocity (cm/sec), Average Aqueduct Area (cm²), Forward Volume (craniocaudal CSF volume, µl), Reverse Volume (caudocranial CSF volume µl), Net Forward Volume (µl), Aqueductal Stroke Volume (µl), Average Flow Rate Per Minute (µl/min).

Statistical Analysis

The data were analyzed using IBM SPSS 23.0 software, and negative velocity values were taken as absolute values because they indicate direction. The format for displaying quantitative change data is [Mean ± Standard Deviation]. To determine the normality of quantitative data's distribution, the Shapiro-Wilk test was utilized. The Mann-Whitney U test was applied based on the normality result. In comparing patient and control groups, age was included as a covariate in the model. Before the ANCOVA analysis, the homogeneity of regression slopes assumption was evaluated by examining the interaction between the covariate and group variables. If the group × age interaction was not statistically significant, it was assumed that the homogeneity-of-regression-slopes assumption was met. In variables for which the assumptions of a normal distribution of residuals and homogeneity of variance were met, age-adjusted group comparisons were performed using univariate ANCOVA. When the assumption of normality of residuals was not met, generalized linear models were used with age as a covariate, and the robust estimator method was preferred for model estimation. Results were presented as adjusted mean ± standard error. To control for the possibility of Type I error arising from multiple tests, the Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to the p-values. A $P < 0.05$ value was perceived as statistically significant.

Power analysis was performed using the G*Power V3.1.9.7 program. Based on the "Mean rate (cm/sec)" result in Table 2 of the reference study, the study was completed with a total of 32 participants with 95% confidence (1-α) and an effect size of f = 0.613, and the power of the study (1-β) was obtained as 91.82% as a result of the post hoc power [14].

Results

The study consisted of 32 cases: 16 POAG patients without other ocular pathology followed in the glaucoma unit of the Ophthalmology outpatient clinic at a university hospital, and 16 healthy individuals (control group) with normal routine eye examinations.

The patient group's mean age was noticeably older than that of controls (Table 1).

In the ANCOVA analysis, age was included as a covariate. The interaction term between the covariate and the group variable was

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examined, and the group × age interaction was not significant. This result indicates that the assumption of homogeneity of regression slopes is met. After controlling for age, the average aqueduct area was 0.043 in the patient group and 0.029 in the control group, with a statistically significant difference between the groups (p = 0.002; Adj. p = 0.024). Accordingly, the average aqueduct area was higher in the patient group than in the control group. This difference remained statistically significant even after FDR correction. In addition, although the ANCOVA mean of the Forward volume variable was higher in the patient group than in the control group, the raw p-value was borderline and did not reach significance after FDR correction (p = 0.050; Adj.p = 0.187). In contrast, no significant differences were found between the patient and control groups in other parameters (Table 2).

Table 1. Demographic characteristics of the cases

Cases group	Age (Mean ± SD)	Gender (Female/Male)
POAG group	59.19 ± 9.46	11/5
Control group	45.44 ± 6.92	10/6

SD: Standard Deviation, POAG: Primary Open Angle Glaucoma

Table 2. Comparison of PC cine MRI parameters of POAG patients and healthy individuals

PC cine MRI parameters	POAG group	Control group	Test statistics	p	Adj.p (FDR)
Average aqueduct area (cm²)	0.043 ± 0.003	0.029 ± 0.002	9.916	**0.002** x	**0.024**
Time to peak flow	665.621 ± 40.009	636.202 ± 34.571	0.293	0.589 x	0.707
Peak velocity (cm/sec)	8.007 ± 0.899	8.457 ± 1.091	0.073	0.788 x	0.799
Average velocity (cm/sec)	0.125 ± 0.041	0.273 ± 0.088	1.920	0.166 x	0.249
Time to peak velocity	635.805 ± 44.847	620.628 ± 37.432	0.065	0.799 x	0.799
Forward volume (µl)	42.745 ± 4.659	27.567 ± 4.659	4.185	0.050 y	0.187
Reverse volume (µl)	41.514 ± 4.460	31.111 ± 4.460	2.145	0.154 y	0.249
Aqueductal stroke volume (µl)	42.115 ± 4.413	29.291 ± 4.413	3.330	0.078 y	0.187
Average flow rate per minute (µl/min)	6.107 ± 0.635	4.259 ± 0.635	3.338	0.078 y	0.187
Net forward volume (µl)	1.231 ± 1.642	-3.544 ± 2.450	2.196	0.138 x	0.249

xGeneralized linear models; yANCOVA; adjusted mean ± standard error; Age considered as a covariate variable; Adj.p (FDR): p-value adjusted using False Discovery Rate method

Discussion

Due to the presence of CSF in the subarachnoid space, IOP and ICP can affect the optic nerve. While the average IOP ranges from 10 to 21 mmHg, the CSF pressure in the subarachnoid space typically measures between 5 and 15 mmHg. [15]. The lamina cribrosa acts as a divider between these two pressure zones. The difference between ICP and IOP is called the translaminar pressure difference, which is usually posterior. [16]. Studies show that patients with POAG have lower ICP than those without glaucoma, and that the etiopathogenesis of glaucoma may be significantly influenced by an increase in the translaminar pressure difference [17]. Since CSF pressure, which can be determined by puncturing the lumbar, is related to ICP, current research uses the terms ICP and CSF pressure interchangeably, as in clinical practice [18].

Volkov et al. noted almost 40 years ago that glaucomatous optic neuropathy may be connected with CSF pressure [5]. According to Yablonsky et al., in normal pressure glaucoma, abnormally low CSF pressure surrounding the optic nerve may result in barotraumatic nerve injury [15].

Berdahl et al. examined the medical records of 31,786 patients retrospectively and discovered that 28 patients with POAG had a lower CFS pressure than 49 patients without glaucoma [19]. Berdahl et al. looked at the records of 62,468 patients with lumbar punctures between 1985 and 2007 in a larger study using the same design. Of these, 57 patients with POAG, 11 patients with normal-tension glaucoma (NTG), a subgroup of POAG, 27 patients with ocular hypertension, and 105 control patients were examined. POAG patients had much lower ICP pressure than the controls (p < 0.0001); NTG patients' ICP pressure was lower than that of the control group (p < 0.001). In addition, the ICP of patients with ocular hypertension was greater than that of the control group (p < 0.05) [16].

Ren et al. prospectively measured CSF pressure in 43 patients with POAG (14 with normal IOP, 29 with increased IOP) and a control group of 71 patients without glaucoma. Lumbar puncture and IOP measurements were performed on all patients on the same day. The translaminar pressure difference (IOP-CSF pressure) was calculated. Both the control group and patients with high pressure glaucoma had considerably higher lumbar CSF pressure than patients with normal pressure glaucoma (p < 0.0001). Patients with both high and normal IOP glaucoma had a significantly greater translaminar pressure difference than the control group. It was determined that the visual field degree loss correlated negatively with CSF pressure and positively with translaminar pressure difference [17].

The possible role of low CSF pressure has been supported by studies in the literature. In this study, based on information about low CSF pressure in patients with POAG, we examined CSF flow parameters at the level of the cerebral aqueduct to detect possible abnormal CSF dynamics in patients with POAG using PC Cine MRI, a non-invasive, contrast-free technique.

PC Cine MRI is a very useful method for qualitative and quantitative evaluation of CSF flow due to its lack of patient preparation, absence of contrast agent, non-invasiveness, and absence of X-ray exposure. In our study, the average aqueduct area was 0.043 cm^2 in glaucoma patients and 0.029 cm^2 in healthy individuals; we found a higher average aqueduct area in glaucoma patients than in healthy individuals ($p = 0.002$). However, there was a significant difference in mean age between the control and patient groups. It was thought that age could affect CSF flow parameters. In an additional ANCOVA analysis, after controlling for age, the average aqueduct area in the patient group was higher than in the control group, and this difference remained statistically significant after FDR correction (Adj. $p = 0.024$). In conclusion, the aqueduct area was higher in patients with POAG than in the control group. This finding may be significant for detecting POAG patients before the onset of symptoms using a non-invasive diagnostic tool, as well as for understanding its impact on the disease prognosis. Given the sample size of this study, repeating it with larger samples may yield new insights into the pathogenesis of POAG.

Bradley et al. calculated the aqueductal stroke volume (ASV) using preoperative PC Cine MRI in patients with normal pressure hydrocephalus who were to undergo shunt surgery. They compared the ASV values with the surgical outcomes. They found that all patients with an ASV value of 42 µl or higher benefited from shunt surgery [20]. Based on the existing studies in the literature, we compared the ASV values in POAG patients, in whom we considered CSF pressure to be low, and in a control group consisting of healthy individuals. We found the mean ASV value (42.115 µl) to be greater in glaucoma patients than in the control group (29.291 µl). However, the two groups did not exhibit a significant difference based on statistical analysis ($p = 0.078$). A study by Ringstad et al. indicated a positive correlation between aqueductal stroke volume and aqueduct area [21]. In our study, the higher ASV values in the patient group were thought to be related to the greater aqueduct area in the patient group. The small sample size in our study may have affected statistical significance. Therefore, studies with larger sample groups are needed.

It has been stated that with increased ICP, CSF flow velocity and output in the aqueduct area increase, and that in patients with idiopathic intracranial hypertension receiving treatment, velocity and output decrease [14]. In our study, the average flow rate per minute and the forward and reverse volumes were higher in glaucoma patients, although not significantly so. However, peak and average velocities were lower in patients with glaucoma. The lower average velocity in glaucoma patients in our study may support the idea that ICP is lower in glaucoma patients. The forward and reverse volumes in our study are thought to reflect the higher aqueduct area in the patient group.

Conclusion

In our study, we compared CSF flow dynamics in patients with POAG and healthy individuals. Instead of measuring CSF pressure with lumbar puncture, an invasive method, we thought that measuring CSF flow parameters with a non-invasive method, PC Cine MRI, could provide valuable information about CSF flow dynamics. We believed that this method could contribute to the early diagnosis of glaucoma patients before the development of ocular symptoms. In our study, statistical analysis between healthy individuals and patients with POAG showed a higher aqueduct area in the glaucoma group. The large aqueduct area may affect CSF flow dynamics in these patients. However, to our knowledge, no studies have used PC Cine MRI in this patient group, so we believe our study can guide future research with larger sample sizes and shed light on broader data in this area.

This study has some limitations. Firstly, the small number of patients may have caused significant differences in parameters to appear insignificant. Another limitation is that the significant age difference between the control and patient groups may have affected CSF flow dynamics.

Ethical Approval
Ethical approval for the study was obtained from the Clinical Research Ethics Committee of İnönü University on 10.01.2018, with decision number 2018/05.

Patient Consent
Before the study began, written and verbal consent was obtained from all from all participants in the study.

Conflict of Interest
The authors confirm the absence of any conflicts associated with this work.

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Thesis Information
This study was derived from the first author's medical specialization thesis.

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