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ORIGINAL ARTICLE

Optimal measurement distance for optic nerve sheath diameter in idiopathic intracranial hypertension via magnetic resonance imaging

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ABSTRACT

Objectives: This study aimed to compare the optic nerve sheath diameter (ONSD) values measured using magnetic resonance imaging (MRI) from 3 mm, 7 mm, and 10 mm behind the orbital globe in patients who met the modified Dandy criteria for idiopathic intracranial hypertension (IIH) with those in a healthy control group.

Patients and methods: This retrospective study examined 88 optic nerves of 44 participants (33 females, 11 males; mean age: 37.3±13.6 years; range, 18 to 67 years) between June 2022 and December 2023. Of these, 21 were patients diagnosed with IIH and 23 were healthy controls. T2-weighted propeller sections were used in the measurements. The ONSD was measured from the optic nerves on both the right and left sides of the globe at 3-, 7-, and 10-mm distances.

Results: Based on receiver operating characteristic analysis findings, ONSD measurements of 3 mm and 7 mm in the right eye were remarkably significant, and 10-mm ONSD measurements were moderately significant in estimating IIH, with area under the curve (AUC) values of 0.889, 0.813 and 0.719, respectively. For the left eye, the 3-mm ONSD measurements displayed substantial results at a high level. In comparison, the 7- and 10-mm ONSD measurements yielded significant results at a moderate level when predicting IIH, with AUC values of 0.816, 0.794, and 0.738, respectively).

Conclusion: Optic nerve sheath diameter measurements were more sensitive to the disease in proximal segments. In the MRI assessment of IIH patients, measurements should predominantly be taken from proximal segments.

Keywords: Cerebrospinal fluid opening pressure, idiopathic intracranial hypertension, magnetic resonance imaging, optic nerve sheath diameter, pseudotumor cerebri.

Idiopathic intracranial hypertension (IIH or pseudotumor cerebri) is a disorder characterized by increased cerebrospinal fluid (CSF) pressure without ventriculomegaly and hydrocephalus, space occupying lesion, and meningeal abnormality.[1] It affects females more than males and has a prevalence of 0.5-2 per 100,000 people.[2] Currently, there remains insufficient information on the causes and etiopathogenesis of the condition, except for its association with the female sex and obesity.[3] The primary indications of the disorder are continual headache,[4,5] which can occasionally be severe, gradual loss of sight,[6] and papilledema, which is observed in almost every patient.[7]

The modified Dandy criteria are used in the diagnosis of the disease, and according to these criteria, patients who are conscious and alert, those who have no localized neurological deficit, those who have a CSF opening pressure higher than 200 mmH_2O, and those who have no

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radiological deformity, displacement, or obstruction in the ventricular system are diagnosed with IIH.[8] In accordance with these standards, the radiological findings that can be observed in this disorder are defined as empty sella turcica, filled CSF spaces within the optic nerve sheath, and venous sinus stenosis or collapse that lacks flow-related irregularities and possesses smooth walls.[9] However, the absence of any positive indirect radiological finding does not exclude the syndrome.[10]

Optic nerve sheath diameter (ONSD) measurements may be one of the most utilized indirect neuroradiological techniques that suggest disease for clinicians, as implied by the modified Dandy criteria. These measurements were made in various magnetic resonance imaging (MRI) and ultrasonography (USG) studies and were associated with IIH. However, to date, criteria that reveal the sensitivity of the values found in indirect neuroradiological measurements to possible or definite disease have not been determined, and there is no consensus.

Therefore, our main purpose was to compare the ONSD values measured using MRI from 3 mm, 7 mm, and 10 mm behind the orbital globe of patients who met the modified Dandy criteria and were diagnosed with definitive IIH due to high CSF pressure with a healthy control group. Thus, we aimed to investigate whether the mean values and values obtained from different distances were sensitive to the disease and at what distance they were more sensitive. The reason for choosing these distances was that there was an opinion that sufficient measurements other than 3 mm and 10 mm have not been made, and that there is ongoing debate regarding the ideal point or points in measurements.[11] We agree with this view and believe that our study may help determine the ideal point(s) for measurements by including multiple distances.

PATIENTS AND METHODS

This retrospective study examined a total of 88 optic nerves from the right and left eyes of 44 participants (33 females, 11 males; mean age: 37.3±13.6 years; range, 18 to 67 years). Of these, 21 were adult patients with IIH who were diagnosed between June 2022 and December 2023 at the headache outpatient clinic of the Kayseri City Hospital, Department of Neurology. These patients were diagnosed according to the modified Dandy criteria, had full neurological and ophthalmological examinations to exclude other diseases, and had their CSF opening pressure measured in lateral recumbent position at the L3-4 interspinal space, with a value of 250 cmH_2O or above. Pressure measurements were made in a single center and by the same neurologist. Patients with a CSF opening pressure between 200 and 250 cmH_2O and requiring clinical reevaluation (grey zone) were excluded from the study since the opening pressure can be found between 200 and 250 mmHg in obese people without IIH.[10] Lumbar puncture was performed 7±5.2 days following brain MRI of patients whose headache met the diagnosis of IIH according to modified Dandy criteria. Brain MRI images of all patients were neurodiagnostically normal, with exceptions noted in the modified Dandy criteria. Moreover, these patients had not received any pressure-lowering treatment before pressure measurement and imaging techniques. The remaining participants were 23 healthy adult volunteers with normal brain MRI and without primary or secondary headache disorders or any focal neurological symptoms, who were randomly included in the control group. These individuals were first examined by a neurologist and then evaluated by an ophthalmologist to exclude eye pathologies. In the control group, those who had any chronic disease such as diabetes mellitus, hypertension, coronary artery disease, systemic autoimmune diseases, episodic or chronic migraine, cluster type headache, psychiatric disorders, chronic renal failure, hyperlipidemia, obesity (determined according to the body mass index [BMI]), or a history of major head trauma or neurosurgical intervention in the last year were excluded. In addition, people using vitamin A supplements, lithium, corticosteroids, tetracyclines (minocycline or doxycycline), antidepressants, antipsychotics, and isotretinoin were excluded. Written informed consent was obtained from all participants. The study protocol was approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Date: 27.09.2023, No: E2-23-5058). The studies were conducted in accordance with the principles of the Declaration of Helsinki.

The ONSD measurements of both the patient and the control groups were made by the same radiologist with an experience of 20 years of brain MRI, who was blinded to the patient and control groups and to the CSF opening values. Siemens MAGNETOM Aera 1.5T MRI device (Siemens

Healthcare, Erlangen, Germany) was used for brain MRI imaging. T2-weighted propeller sequences were used in the measurements. A 24-channel head coil was used in the MRI technique, and 5-mm slices were used in radiological evaluation. To enhance measurement accuracy, standard size images were magnified threefold using the magnifying glass feature in the picture archiving and communication system (PACS) software to enable a more detailed evaluation of the globe and surrounding structures. The same brightness and contrast levels were selected for the windows used in the evaluation. The ONSD was measured from the optic nerves on both the right and left sides of the globe at 3 mm, 7 mm, and 10 mm distances (Figure 1). In selecting these distances, the most frequently preferred distance to date (3 mm), the most distal distance preferred to date (10 mm), and a point between these two distances (7 mm) were taken into consideration. The reason for taking measurements from 7 mm was to determine whether sensitivity comparisons were made proximally or distally and not just between two points. The mean values, both overall and at each distance in millimeters, were compared between the two groups.

Statistical analyses

The statistical analysis of the data was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequency (n) and percentage (%). Technical abbreviations were explained upon their first use. Descriptive statistics were reported as mean ± standard deviation (SD) for normally distributed numerical data, and as median (min-max) with mean±SD for nonnormally distributed numerical data. The study used the chi-square test to compare the proportions of categorical variables. To evaluate the normality assumption of numerical data, the Shapiro-Wilk test, histograms, and Q-Q plots were performed, along with Levene's test, to assess the homogeneity of variances. Student's t-test was employed to compare continuous data of two independent groups when parametric test assumptions were met, and the Mann-Whitney U test was used when these assumptions were not met.

Receiver operating characteristic (ROC) analyses were conducted to assess the potential of ONSD measurements as prognostic markers for predicting IIH. Receiver operating characteristic curves and the calculation of the area under the curve (AUC) were performed, including 95% confidence intervals. Area under the curve values were classified as follows: 0.9-1 (excellent), 0.8-0.9 (good), 0.7-0.8 (fair), 0.6-0.7 (weak), and 0.5-0.6 (poor). The Youden index, which maximizes sensitivity and specificity, was used to determine the optimal cut-off point in ROC analyses. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) measurements were used to evaluate the performance of these cut-off points. For all comparisons, a p-value <0.05 was considered statistically significant.

RESULTS

The mean pressure value of the patients in the IIH group was 373.8±98.9 (range, 250 to 700) mmHg. Statistical findings related to the comparison of sex, age, and right and left eye 3-, 7-, and 10-mm and mean ONSD measurements

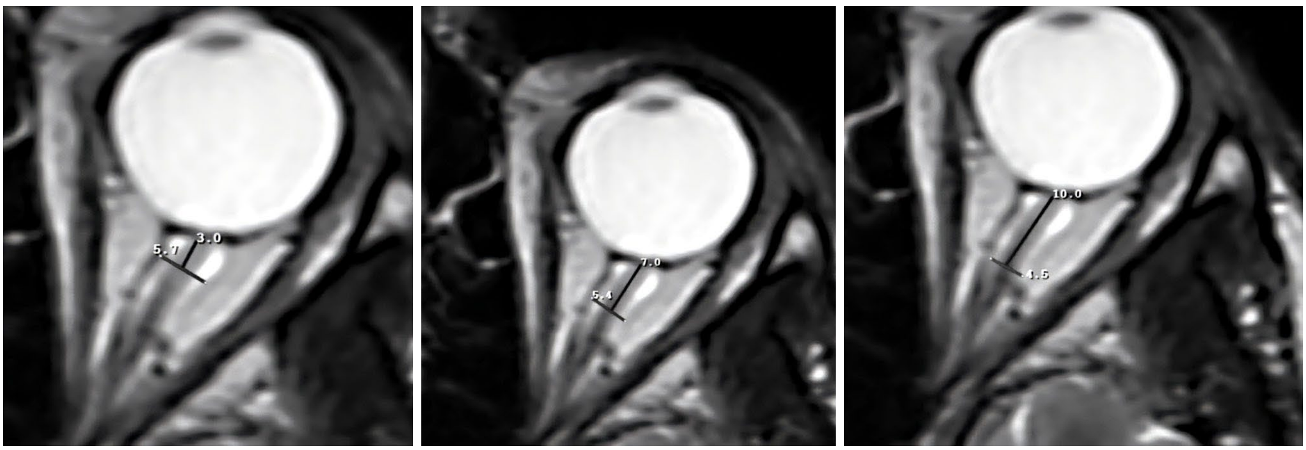

Figure 1. Measurement of ONSD from 3, 7, and 10 mm.

TABLE 1
Comparison of age, sex, and ONSD measurements between patients with IIH and controls

	Control (n=23)					Case (n=21)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			34.8±15.1					40.1±11.4			0.202b
Sex											**0.862a**
Male	6	26.1				5	23.8				
Female	17	73.9				16	76.2				
ONSD right eye (3 mm)			3.8±0.93					5.54±1.25			**<0.001c**
ONSD right eye (7 mm)			3.76±0.92	3.6	2.4-5.7			4.98±1.25	4.8	3.5-9.5	**<0.001d**
ONSD right eye (10 mm)			3.65±0.68	3.6	2.2-4.7			4.4±1.13	4.1	2.9-8.5	**0.013d**
ONSD left eye (3 mm)			4.24±0.81					5.52±1.17			**<0.001c**
ONSD left eye (7 mm)			3.92±0.72	3.9	2.4-5.2			4.95±1.12	4.8	3.1-8.1	**0.001d**
ONSD left eye (10 mm)			3.6±0.67	3.5	2.6-4.9			4.33±0.98	4.2	2.7-7.5	**0.007d**
Average of ONSD for the right eye			3.73±0.78	3.6	2.3-5.3			4.97±1.19	4.6	3.4-9.1	**<0.001d**
Average of ONSD for the left eye			3.92±0.65					4.93±1.06			**<0.001c**

ONSD: Optic nerve sheath diameter; IIH: Idiopathic intracranial hypertension; SD: Standard deviation; a: Chi-square test; b: Student's t-test (Welch t-test for unequal variance); c: Student's t-test; d: Mann-Whitney U test.

between the research groups are presented in Table 1. The sex distribution was similar between the groups (p=0.862). There was no statistically significant difference between the mean age of the IIH group (40.10±11.40) and the control group (34.83±15.13; p=0.202, Table 1).

The right eye 3-, 7-, and 10-mm ONSD measurements of the IIH group were significantly higher than those of the control group (p<0.001, p<0.001, p=0.013, respectively; Table 1). The left eye 3-, 7-, and 10-mm ONSD measurements of the IIH group were significantly higher than those of the control group (p<0.001, p=0.001, p=0.007, respectively; Table 1). The mean ONSD measurements for both the right and left eyes of the IIH group at 3, 7, and 10 mm were significantly higher than those of the control group (p<0.001, p<0.001, respectively; Table 1).

TABLE 2
The ROC analysis findings demonstrate the success of right and left 3-, 7-, and 10-mm ONSD measurements in distinguishing patients with IIH and controls

Measurements	AUC	95% CI
ONSD right eye 3 mm	0.889	0.796-0.982
ONSD right eye 7 mm	0.813	0.685-0.940
ONSD right eye 10 mm	0.719	0.565-0.874
ONSD left eye 3 mm	0.816	0.686-0.945
ONSD left eye 7 mm	0.794	0.658-0.930
ONSD left eye 10 mm	0.738	0.586-0.890
Average of ONSD for the right eye	0.839	0.720-0.957
Average of ONSD for the left eye	0.808	0.676-0.941

ROC: Receiver operating characteristic; ONSD: Optic nerve sheath diameter; IIH: Idiopathic intracranial hypertension; AUC: Area under curve; CI: Confidence interval.

Table 2 shows the AUC values and 95% confidence intervals derived from the ROC analysis to determine the effectiveness of the ONSD measures in predicting IIH. Figure 2 displays the ROC curves as well. Based on the ROC analysis findings, ONSD measurements of 3 mm and 7 mm in the right eye were remarkably significant, and 10 mm ONSD measurements were moderately significant in estimating IIH, with AUC values of 0.889, 0.813, and 0.719, respectively, as indicated in Table 2. Thereafter, we advised that these measurements be utilized as significant markers in future prediction models. For the left eye, the 3-mm ONSD measurements displayed significant results at a high level, while the 7- and 10-mm ONSD measurements yielded significant results at a moderate level when predicting IIH, with AUC values of 0.816, 0.794, and 0.738, respectively, as shown in Table 2. Additionally, the mean ONSD measurements for both the right and left eyes demonstrated significant results at a high level in predicting IIH, with AUC values of 0.839 and 0.808, respectively, as shown in Table 2.

Figure 3 presents box plots illustrating the distribution of 3-mm ONSD (optic nerve sheath diameter) measurements and the optimal cut-off

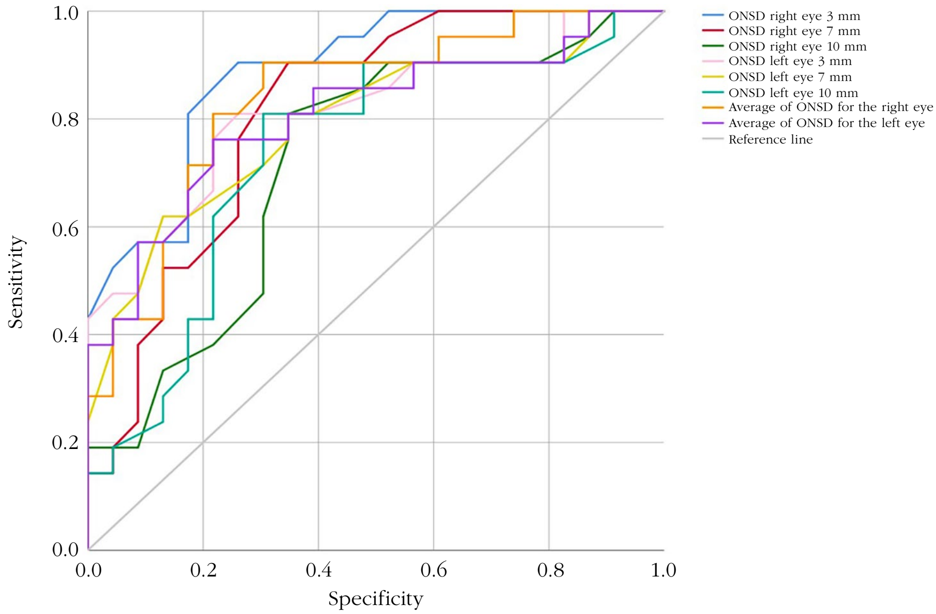

Figure 2. ROC curves demonstrate the success of right and left 3-, 7-, and 10-mm and mean ONSD measurements in distinguishing patients with IIH and controls.

ROC: Receiver operating characteristic; ONSD: Optic nerve sheath diameter.

points with the highest AUC values for both the right and left eyes. The optimal cut-off point for the right eye was determined to be 4.35 mm, yielding a sensitivity of 90.5% (95% CI: 68.1-98.3), specificity of 73.9% (95% CI: 51.3-88.9), positive predictive value (PPV) of 76.0% (95% CI: 54.5-89.8), and negative predictive value (NPV) of 89.5% (95% CI: 65.5-98.2). For the left eye, the optimal cut-off point was calculated as 4.65 mm, with a sensitivity of 81.0% (95% CI: 57.4-93.7), specificity of 73.9% (95% CI: 51.3-88.9), PPV of 73.9% (95% CI: 51.3-88.9), and NPV of 81.0% (95% CI: 57.4-93.7).

DISCUSSION

In this study, it was observed that ONSD exhibited significantly thicker measurements in the patient group compared to the control group.

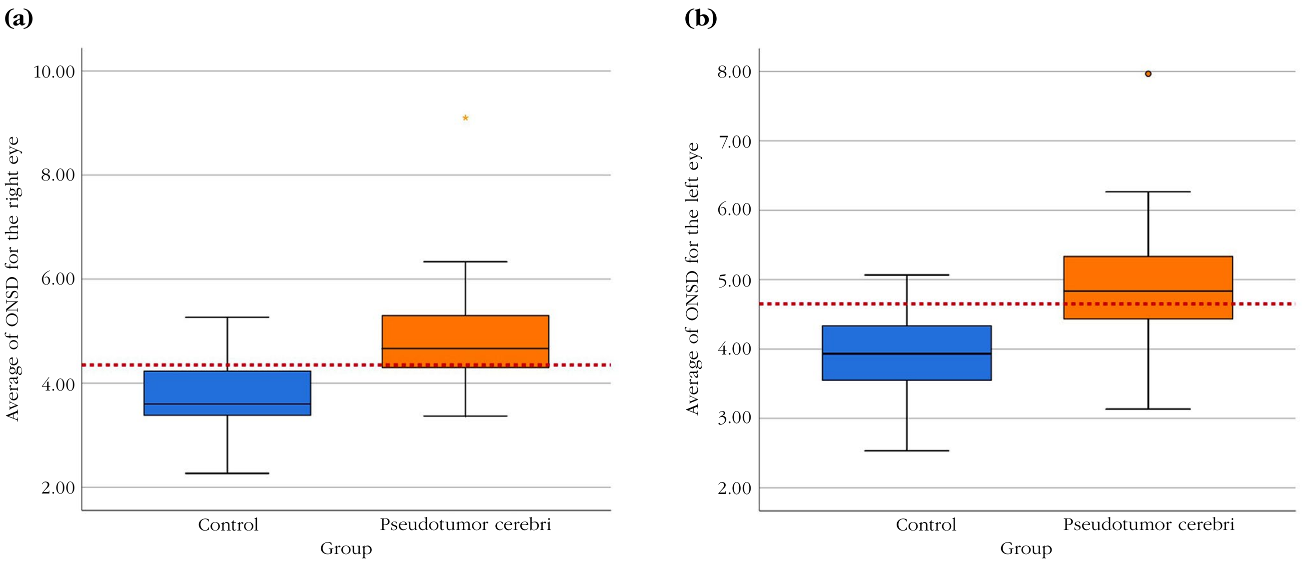

Figure 3. Box plot displaying the distributions and optimal cut-off points for the right 3 mm **(a)** and left 3 mm **(b)** measurements of the ONSD.

ONSD: Optic nerve sheath diameter.

Furthermore, it was demonstrated that ONSD's high-pressure sensitivity was particularly conspicuous at 3 mm and 7 mm for the right side and 3 mm for the left side. However, the sensitivity of ONSD thickness values obtained at 10 mm to the posterior globe on the right side and 7 mm and 10 mm on the left side was less sensitive. At the same time, we found the upper limit of 4.35 mm for the right eye and 4.65 mm for the left eye as a threshold point in sensitivity in measurements made from 3 mm.

In the literature, studies investigated the correlation between measured pressure and ultrasonographic ONSD in trauma and intensive care patients, or in patients with increased intracranial pressure due to an unspecified reason, and reported a positive correlation.[12] For example, Chen et al.[13] reported that ultrasonographic ONSD was sensitive to intracranial pressure, regardless of the underlying physiopathological mechanisms. Raboel et al.[14] stated in a review study that noninvasive transorbital ultrasound techniques were useful in intracranial pressure, but they were not superior to invasive techniques. However, the main handicap in these studies was that diseases with different underlying physiopathological mechanisms (for example, mass, traumatic subdural hematoma, acute middle cerebral artery infarction, central nervous system infection, and IIH) were evaluated in the same group.[15] These studies may not provide guidance for IIH due to the incomplete understanding of the physiopathological process in IIH and the exclusion of space-occupying lesions and focal or multifocal neurodiagnostic findings in the modified Dandy criteria. Because the methodologies used are different from studies examining specifically IIH patients and have a high potential to influence the results.

To date, studies investigating ONSD in IIH were mainly based on USG. Aslan et al.[16] reported that there was a positive correlation between the CSF opening pressure and ONSD measured at 3 mm in pediatric IIH patients. Researchers reported that this correlation was valid in both the right and left eyes. Bozdogan et al.[17] similarly demonstrated that measurements made from 3 mm were sensitive to increased pressure, and the measured values decreased rapidly following lumbar puncture. In another review study, 15 published USG studies were evaluated, and it was concluded that ONSD was a useful technique in IIH.[18] In all the articles evaluated in this analysis, measurements were made from 3 mm. However, it is difficult to make a definitive opinion about the exact distance at which ONSD is sensitive, as ultrasonographic measurements are user-dependent. Furthermore, measurements from different distances have not been evaluated in USG-based studies for various reasons. Ultrasonography is not technically sufficient for objective evaluation of distal measurements, and therefore, USG-based studies have constantly used 3-mm methodologically and have not provided information about the sensitivity of more distal measurements. Therefore, computed tomography (CT) or MRI studies, which are less user-dependent and allow measurement from different distances, have also been on the agenda recently.

In a CT-based study, it was found that the ONSD thickness was significantly greater in patients with IIH compared to the control group.[19] However, this study lacked sufficient data on the specific distance from which ONSD was measured behind the globe. Another CT study, which measured ONSD from the intersection of the ophthalmic artery and optic nerve, also found higher measurements in the patient group.[20] Anatomical variations in the ophthalmic artery were not considered in this study. Instead, the optic nerve-ophthalmic artery intersection point was determined as a landmark, so measurements were taken from a fixed anatomical point in each subject.[21]

In our study, we observed differences in the ONSDs of the right and left eyes. A possible explanation is that there may be slight asymmetries in the human body, and the visual load of the dominant eye may be greater, potentially contributing to asymmetry in ONSD.[22]

In the normative study conducted by Vaiman et al.,[11] optic nerve sheath measurements were performed at 3 mm and 10 mm using CT. In this study, it was demonstrated that measurements taken at 3 mm showed significant variability due to the continuous movement of the eyeball. Therefore, it was determined that measurements taken at 10 mm could provide more accurate results. However, unlike our study, they utilized CT and did not include a comparison with patients with increased intracranial pressure.

In a review study, ONSD thickness on MRI was analyzed in four published articles, and it was claimed that this finding was sensitive to the disease.[23] However, since both the methods and the statistical analyses used by the studies discussed differed, no definitive opinion could be expressed about the measurement distance. One MRI study examined the subarachnoid space increase around the optic nerve as a potential ailment, but its measurements did not encompass varying distances.[24] The study also compared this radiological discovery with other indirect findings, including flattening of the globe, optic nerve tortuosity, and optic nerve protrusion. Patterson et al.[25] investigated patients with papilledema and pseudo-papilledema using both USG and MRI. The measurements were taken from a distance of 3 mm behind the globe, and the findings demonstrated that there was no superiority of one imaging method over the other. The latter study was based on a methodology quite different from our study, as it compared the sensitivity of MRI and USG images. Nevertheless, researchers suggested that an empty sella detected on MRI could enhance diagnostic specificity.

To our knowledge, the only study to date measuring the posterior globe ONSD from different distances with MRI was conducted by Ertekin et al.[26] In this study, ONSD was measured from 3 mm and 10 mm behind the globe in both eyes, and proximal measurements were found to be more sensitive and specific than distal measurements. Researchers stated that there was sensitivity to the disease at both 3 mm and 10 mm and that proximal measurements were statistically more valuable. However, unlike our methodology, they included a control group from the neurosurgery clinic rather than healthy individuals. Furthermore, whether the patients had head trauma or other pathologies was not specified, and, moreover, the definitive diagnoses of IIH patients based on pressure measurements were not written in the methods section.

We believe that ONSD measurements of patients with IIH will be made more frequently with MRI in the future, as it is easier to make measurements from different distances with MRI, and as it is less user-dependent than USG. Moreover, MRI easily provides ONSD, optic nerve tortuosity, posterior flattening of the globe, optic nerve protrusion, and the empty sella sign to radiology and neurology specialists in a single session. However, whether it can replace the opening CSF pressure measured via lumbar puncture remains debatable. For this reason, to avoid invasive methods, artificial intelligence applications that evaluate MRI data may need to be used more in the future. For example, in subjects who are clinically suspected of having the disease by a neurologist or ophthalmologist, indirect MRI findings with proven sensitivity can be evaluated with appropriate software, and brain MRI findings in papilledema and pseudo-papilledema can be differentiated.

The present study is the second MRI study in the literature that measures ONSD from different distances. This study aimed to find out at which distance the sensitivity was greater by measuring the ONSD thickness at 3 mm, 7 mm, and 10 mm and comparing it in both groups. The results suggested that proximal measurements were more valuable. Furthermore, we revealed that the disease might be found in distal or total/mean measurements. However, due to its high sensitivity, we recommend using the behind globe distance of 3 mm for measurements made using MRI.

The main limitations of our study were the small number of patients and controls included and the fact that we did not compare other indirect radiological findings mentioned in the modified Dandy criteria with ONSD measurements made from different distances. Future studies that combine empty sella turcica, venous stenosis, or collapse with ONSD measurements taken from 3 mm from the posterior globe could increase the radiological sensitivity for the disease. Furthermore, measurements from distances further than 10 mm were not included in this study, although it is questionable whether these measurements would make a difference. Few studies have reported a correlation between BMI and ONSD in healthy people. However, our selection of nonobese individuals according to BMI into the control group did not make it possible to evaluate the controls from this perspective. In this respect, further studies using patient and control groups matched according to BMI are needed.[27] Of course, one may ask why the measurements were not compared with a standard thickness. However, since the millimeter limits of ONSD in healthy people have not yet been strictly determined, it currently remains more appropriate to compare ONSD with those of a control group rather than with a certain thickness value. On the other hand, we found that the cut-off value for disease sensitivity in posterior globe 3-mm measurements was 4.35 mm for the right eye and 4.65 mm for the left eye. However, studies involving larger numbers of patients and controls are needed to confirm these values. Another limitation of the study may be that the control group's evaluation was made solely on clinical examination without a lumbar puncture. Lastly, the ratio of the eyeball diameter to the ONSD at distances of 3, 7, and 10 mm was not measured, which could have increased the sensitivity and reliability of the results.

In conclusion, this study measured ONSD from both sides in patients with IIH using MRI from different distances behind the globe, including 3 mm, 7 mm, and 10 mm, and identified the distance that was most sensitive to the disease. Our findings suggested that in the MRI assessment of patients with IIH, ONSD measurements should predominantly be taken from proximal segments. As measurements were taken more proximally (from 3 mm or between the 3 and 7 mm interval), there was an increase in the indirect radiological findings that suggest the presence of the disease. Nevertheless, further studies are needed to determine the ideal distance or distances.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: F.E., M.A.; Design, control/supervision: F.E., O.Ö.; Data collection and/or processing: O.Ö., G.T., M.A.; Literatur review: G.S., M.A., G.T.; Writing the article: F.E., G.S., M.A.; Critical review: M.A., G.S.

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